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Cognitive Impairment in Men With Testicular Cancer Prior to Adjuvant Therapy

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Abstract

BACKGROUND: Cognitive dysfunction experienced by individuals with cancer represents an important survivorship issue because of its potential to affect occupational, scholastic, and social activities. Whereas early efforts to characterize cognitive dysfunction primarily focused on the effects of chemotherapy, more recent evidence indicates that impairment may exist before systemic treatment. This study characterized cognitive dysfunction before adjuvant chemotherapy in a sample of men diagnosed with nonseminomatous germ cell tumors (NSGCT) of the testis.

METHODS: Men with newly diagnosed NSGCT were recruited after orchiectomy but before adjuvant chemotherapy. Patients completed neuropsychological tests to assess attention, learning, language, executive function, and motor function. Self-report measures of depression and anxiety were also administered. An overall cognitive function index was computed for participants. Cognitive impairment was defined as a *z*-score of less than or equal to −1.5 on 2 or more tests, or a *z*-score of less than or equal to −2.0 on a single test.

RESULTS: Approximately 46% of patients exhibited cognitive impairment at the time of assessment, which is significantly greater than would be expected considering healthy population norms (binomial test: $P < .0001$). Patients exhibited impairments in motor function, verbal learning, and executive function much more frequently relative to normative expectations (binomial test: $P < .0001$).

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CONFLICT OF INTEREST DISCLOSURES

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CONCLUSIONS: The prevalence of cognitive impairment in men with newly diagnosed NSGCT is unexpectedly high before the receipt of adjuvant chemotherapy. Efforts to track cognitive function over time and to develop effective interventions are warranted.

Keywords

cognition disorders; testicular neoplasms; orchiectomy; quality of life

Cognitive dysfunction in cancer patients is receiving increased attention as a survivorship issue due to its potential to interfere with occupational, scholastic, and social activities. Cognitive dysfunction reported during or after chemotherapy has been labeled ‘‘chemobrain’’ by the survivorship community. However, evidence for cognitive dysfunction before receipt of chemotherapy has been reported for patients with breast cancer,[1–4] prostate,[5] and small cell lung cancer.[6] Recognition of cognitive dysfunction before systemic treatment has underscored the need to design longitudinal studies of treatment-related cognitive dysfunction with pretreatment baseline evaluations.[1,7] Whereas many studies have concentrated on women with cancer, men with cancer appear to be at risk for similar disease-related cognitive dysfunction.

Germ cell tumors are the most common malignancy in men aged 15 to 34 years.[8] Nonseminomatous germ cell tumors (NSGCT) are the second most common form of testicular tumor.[9] They differ from seminomas in that they often present as more advanced disease (eg, stage II and III), metastasize earlier and frequently via hematogenous route, are less radiosensitive, and generally have a poorer prognosis.[10] Fortunately, stage I NSGCT disease has been associated with nearly 100% survival,[8] while stage III disease is reported to be curable in approximately 70% of patients. Prognosis related to location of the primary tumor (gonadal or extragonadal), extent of disease, and tumor aggressiveness is determined by degree of elevation in the following tumor markers: alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG), and lactase dehydrogenase (LDH).

Given the relatively good survival of many testicular cancer patients, it is of critical importance to understand the nature, extent, and temporal course of disease-related symptoms and treatment-related toxicities. Characterizing the incidence, pattern, and predictors of cognitive dysfunction in NSGCT patients before adjuvant therapy is warranted to determine cognitive deficits, inform prospective trial designs, and ascertain proper intervention.

MATERIALS AND METHODS

Study Site and Participants

Patients were recruited from the genitourinary medical service of The University of Texas M. D. Anderson Cancer Center, Houston, Texas. To be eligible for study enrollment, patients were required to meet the following criteria: 1) newly diagnosed with NSGCT, 2) between age 18 and 50, 3) English speaking and writing, and 4) able to provide informed consent. Patients with prior or existing neurological illness (including closed head injury and brain metastasis), primary extragonadal germ cell tumor, or major psychiatric illness were

considered ineligible. Between December 1999 and December 2002, 280 consecutive patients with testicular cancer were screened, and 100 were found to meet the eligibility criteria. Seventy-six of these men consented to the study, and 69 completed the baseline neurocognitive assessment.

Procedures

A systematic, consecutive sampling procedure was used to identify potential participants. Patients with newly diagnosed testicular cancer were identified from daily reviews of clinic schedules. Research staff then thoroughly reviewed each patient's medical records foreligibility criteria. Eligible patients were recruited to the study after orchiectomy but before adjuvant treatment. At the time of study enrollment, participants completed a baseline assessment consisting of cognitive tests and self-report measures. Similar assessments were completed 1 week following the completion of adjuvant chemotherapy, or 3 months after baseline assessment for participants who did not receive adjuvant chemotherapy. The final assessment was completed 12 months after baseline assessment. The study was approved by the institutional review board of The University of Texas M. D. Anderson Cancer Center. This study reports the findings from the baseline assessment.

Measures

A battery of 6 neuropsychological tests designed to tap multiple cognitive domains was administered (Table 1), including attention, psychomotor speed, learning and memory, language, executive, and motor function. Published normative data that adjust for age, education, handedness, and sex (where appropriate) were used to convert raw cognitive test scores to standardized scores (*z*-scores; mean = 0, SD = 1) to facilitate comparisons.

The self-report assessment consisted of sociodemographic variables including age, education level, race/ethnicity, marital status, and psychosocial measures. Depressive symptoms were assessed with the Centers for Epidemiologic Studies – Depression (CES-D) scale[11] and anxiety was assessed using the State-Trait Anxiety Inventory (STAIS).[12] Clinically significant symptoms of distress (ie, depressive or anxious symptoms) were operationally defined as ratings on the CES-D ≤27 (raw score) and STAIS ≤fifth percentile. Evidence from medically ill populations suggests the cutoff score of 27 on the CES-D; this method provides better sensitivity and specificity compared with other commonly used cutoffs (eg, 16).[13,14] Additional psychosocial tests (eg, health-related quality of life, social support, and sexual function) were also administered but not included in the current analysis. The entire assessment required approximately 60 minutes to complete.

Disease stage and tumor marker (ie, AFP, hCG, and LDH) data were collected through medical record abstraction. Staging was determined using the American Joint Committee on Cancer Staging for Testicular Germ Cell Tumors criteria.[15] Risk categories were determined as defined by the International Germ Cell Cancer Collaborative Group.[16]

Statistical Analysis

As described previously,[1] an index for each patient's baseline overall cognitive function (OCFI) was operationally defined as impaired (OCFI-I) or not impaired (OCFI-NI) using a

2-part criterion[1]: if a patient performed at a z-score of ≤ −1.5 on 2 or more tests, or[2] if they performed ≤ −2.0 on a single test they were classified as OCFI-I. All other patients were classified as OCFI-NI. This 2-step approach was designed to minimize the number of potential false-positive errors resulting from multiple tests and to determine the frequency of impairment rather than low performance. In a normal, healthy population, −1.5 and −2.0 standard deviations below the mean correspond to performances at the seventh and second percentiles, respectively. By using curves based on the binomial probability distribution,[17] we determined that in a battery of 6 independent tests approximately 12% of the population will perform 2 SDs below the mean on a single measure and 5% would perform 1.5 SDs below the mean on 2 measures. Thus, if the rate of impairment was equal to or greater than the upper limit of 12%, it was considered significant.

Descriptive statistics (means, medians, standard deviations, and frequencies) were generated for the sociodemographic and clinical variables. Relationships between neurocognitive function and selected demographic and clinical variables were then examined using adjusted and unadjusted procedures. Bivariate associations between standardized cognitive test results and measures of affective distress and other predictors were evaluated with Pearson correlations. Multivariate linear regression was used to evaluate the independent effects of the predictor variables associated with each cognitive test. Logistic regression was used to model the relationship between OCFI and predictor variables. The OCFI and cognitive tests were regressed on the linear combination of demographic and psychological variables. For each cognitive outcome a final model of main effects was obtained using stepwise selection; a cutoff of $P < .05$ was used to retain variables for inclusion in the final model.

Results of the linear regression were summarized using total variance explained by the final model, R^2 values, regression estimates, and 95% confidence intervals (CI). Results of the logistic regression were summarized using adjusted odds ratios (OR) and 95% confidence intervals. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC) and SPSS 12.0 (SPSS, Chicago, IL).

RESULTS

Sixty-nine patients with a diagnosis of Stage I (n = 35; 51%), Stage II (n = 23; 33%), or Stage III (n = 10; 15%) NSGCT underwent neuropsychological evaluation after orchiectomy (mean, 44 ± 38 days after orchiectomy) and before beginning chemotherapy (staging information was unavailable for 1 patient). No patient received radiation therapy. The mean age was 31.0 (±7.5) years (range, 18.5–50.7 years). On average, patients had completed (±2.7) years of education (range, 8–20 years). Ethnically, 52 (75%) patients were Caucasian, 12 (17%) were Hispanic, 3 (4%) were African American, 1 (1%) was an Asian/Pacific Islander, and 1(1%) was an Other.

Using the OCFI classification criteria described above, approximately 46% of patients (32 of 69 patients; Binomial test: $P < .0001$) received a classification of OCFI-I before initiation of adjuvant therapy. Approximately 14% (10 of 69) exhibited impairment on 1 test (as a result of having a z score less than or equal to −2.0), whereas approximately 32% (22 of 69) exhibited impairment on 2 or more tests (as a result of having a z score less than or equal to

−1.5). Men with NSGCT exhibited impaired dominant hand fine motor dexterity (GPD; Binomial test: $P < .0001$), verbal learning (HVLT; Binomial test: $P < .0001$), and executive function (TMTB; Binomial test: $P < .0001$) significantly more frequently relative to normative expectations (Table 2).

On self-report measures, 10% of patients (7 of 69) reported clinically significant symptoms of depression and 7% of patients (5 of 69) endorsed clinically significant symptoms of anxiety. Pearson correlations between cognitive variables and mood measures revealed that CES-D scores were significantly correlated with WAIS-R DSymbol scores, HVLT T1–3, and TMTB (Table 3). STAIS scores were significantly correlated with HVLT T1–3. Chi-square analysis revealed statistically significant relations between clinicaldepression or anxiety and OCFI status. In addition, no other significant associations between mood and cognitive function were detected.

In addition to depression and anxiety, the following variables were assessed as possible predictors of neurocognitive function: age, years of education, stage of disease, depression, anxiety, time since surgery, and specific biomarkers. Standardized cognitive test scores were analyzed as continuous outcomes. Pearson correlations between each cognitive test and predictor variables are summarized in Table 3. Years of education were significantly associated with all outcomes except COWA and GPD. Age was significantly associated with TMTB and WAIS-R DSpan. AFP was significantly associated with TMTA.

Results of the stepwise linear model were summarized using beta (β) coefficients and 95% CIs. After adjustment for other covariates, years of education was significantly associated with the following outcomes: WAIS-R DSymbol: R^2, 0.53; β, 0.54; 95% CI, 0.31–0.78 ($P < .01$); WAIS-R DSpan: R^2, 0.44; β, 0.40; 95% CI, 0.16–0.64 ($P < .01$); TMTB: R^2, 0.26; β, 0.41; 95% CI, 0.21–0.62 ($P < .01$); and HVLT T1–3: R^2, 0.10; β, 0.16; 95% CI, 0.02–0.30 ($P < .05$). In addition, WAIS-R D Symbol was significantly associated with CES-D (R^2, 0.53; β, −0.17; 95% CI, −0.28 to −0.07; $P < .01$) and STAIS (R^2,0.53; β, 1.1; 95% CI, −2.0 to −0.24; $P < .05$). OCFI status was analyzed with logistic regression. Results of the stepwise logistic model were summarized using adjusted ORs and 95% CIs. After adjustment for other covariates, only years of education was significantly associated with OCFI status such that, for every year less of education, the adjusted OR is 0.63 (adjusted OR, 0.63; 95% CI, 0.47–0.85; $P < .01$).

DISCUSSION

Before receipt of adjuvant therapy, 46% of men with NSGCT demonstrated impaired cognitive function (OCFI-I). Cognitive impairment, as defined by the OCFI-I criteria, was associated with fewer years of education. Across all cognitive tests, impairments were most frequent on measures of learning and memory, executive function, and upper extremity, fine motor dexterity. After adjusting for other covariates, years of education was related to measures of learning and memory as well as executive function, but not upper extremity, fine motor dexterity. While measures of psychomotor speed were associated with depression and anxiety, no other cognitive domain was associated with affective distress. In addition, no

cognitive domain was associated with time since surgery, stage of disease, or levels of alpha-fetoprotein, lactase dehydrogenase, human chorionic gonadotrophin, or testosterone.

With the exception of education, many clinical (eg, fatigue, stage of disease, surgery type), mood (eg, anxiety, depression), and quality of life variables appear to have limited impact on cognitive function.[1,2,4,7,18–21] Given that these factors do not seem to account for the development of cognitive impairment in this study, future investigations to explore additional biomarkers (such as inflammatory cytokines) are indicated. Limited investigation into cytokine activity associated with testicular cancers has been conducted.[22] However, an established body of research has demonstrated the relationship between cytokines and a variety of symptoms including cognitive dysfunction in other cancer populations.[23–26] It is also possible that the pattern of memory, executive function, and motor abnormalities observed in our study may be related to a subclinical, autoimmune paraneoplastic process. Several papers have described paraneoplastic limbic encephalitis in men with testicular cancer associated with anti-Ma and anti-Ta antibodies.[27–30] Although our consent rate was quite good (76%) for this relatively rare tumor type, the current sample derived from a large tertiary cancer center may not be entirely representative of all NSGCT patients. However, we believe that our findings make an important contribution to the literature in this population.

To date, 3 retrospective studies of cognitive function in testicular cancer survivors have been reported.[21,31,32] Gritz et al[31] assessed testicular cancer survivors (seminoma and nonseminoma) who had received mixed treatments an average of 45 months earlier. Of these survivors, 14%−16% self-reported inability to concentrate, think clearly, and complete tasks 6 months following treatment, which was much more frequent than either before diagnosis or within the past month. Pedersen et al[32] reported results from a mixed sample that received either surgery alone or surgery and radiotherapy, and thus are not comparable to our study population. Schagen et al[21] reported cognitive dysfunction in 5.5% of testicular cancer survivors who were tested a median of 3years after surgery and received no other adjuvant therapy. There was no relationship between cognitive impairment and fatigue, depression or anxiety. Unfortunately, they did not present any data on cognitive test results, so it cannot be determined which domains of cognition were affected.

Our study found a greater prevalence of cognitive dysfunction in men with testicular cancer after surgery and before adjuvant therapy compared with healthy population norms. However, comparison with Schagen et al[21] is difficult because of several critical methodological differences. The difference in prevalence likely reflects differences in the criteria used to define cognitive dysfunction, and may also reflect the use of different cognitive tests and different assessment time points after surgery. We determined impairment relative to healthy population norms, thus reflecting the prevalence of impaired cognitive performance relative to each patient's preillness level of expected performance. In contrast, Schagen et al[21] defined impairment as the lowest performing 5% of the surgery-alone group, thereby restricting their observed prevalence rate of cognitive impairment to 5%. Moreover, they did not use data from healthy normal controls to determine the degree to which these men performed below preillness expectations. Our study also assessed patients more acutely postoperatively. We did not detect a relationship between time since surgery and cognitive

impairment, but because our patients were seen between 6 days and 6 months after their orchiectomy, our findings may not be generalizable to the longer postsurgery period in Schagen et al.[21]

The use of different cognitive tests by different investigators (often in different countries), different standardization samples, and different operational definitions of cognitive impairment has made direct comparisons between studies of cognitive function in cancer patients particularly challenging. Recently, the International Cognition and Cancer Task Force has attempted to reach consensus on a core approach to assessing cognitive function that would be amenable to international comparisons.[33] However, these guidelines are still in development and have not been integrated into current research studies.

The prevalence of cognitive impairment in men with NSGCT found in this study is unexpectedly high. These men are generally young and in the midst of their occupational careers, often with young families and in social circumstances that require optimal cognitive functioning. It is important to be aware of possible adverse effects of cancer itself on job functioning, family activities, and other social obligations. Psychosocial support and compensatory interventions may be necessary in a subset of patients with especially disabling symptoms. Longitudinal studies that determine the persistence and functional impact of these cognitive deficits, as well as predictive biomarkers, will be crucial in determining the relative contributions of the disease and various treatments to cognitive function, and to inform intervention strategies.

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Table 1.

Neuropsychological Tests Grouped by Principle Cognitive Domain and Biomarkers

Domain	Test Name	Abbreviation
Attention	WAIS-R Digit Span[34]	WAIS-R DSpan
Psychomotor speed	WAIS-R Digit Symbol[34]	WAIS-R DSymbol
	Trail Making Test Part A[35]	TMTA
Language	MAE Controlled Oral Word Association[36]	COWA
Learning and memory	HVLT Trials 1–3, Total Recall[37]	HVLT T1–3
Executive function	Trail Making Test Part B[35]	TMTB
Motor	Grooved Pegboard[38] (Dominant hand)	GPD
	Grooved Pegboard (Non-Dominant hand)	GPND
Depression	Center for Epidemiologic Studies Depression Scale[11]	CESD
Anxiety	State-Trait Anxiety Inventory- State score[12]	STAIS
Biomarkers	Human chorionic gonadotropin	HCG
	Alpha-fetoprotein	AFP
	Lactate dehydrogenase	LDH
	Testosterone	TESTOS

WAIS-R indicates the Wechsler Adult Intelligence Scale-Revised; HVLT, Hopkins Verbal Learning Test; MAE, Multilingual Aphasia Examination; Grooved Pegboard, Lafayette Grooved Pegboard.

Table 2.

Mean Score and Impairment Frequency at Baseline on Each Test, Grouped by Principle Cognitive Domain (n = 69)

Cognitive Domain	Mean±SD	% Impaired
Attention		
WAIS-R DSpan[a]	9.8 (2.6)	4.3
Psychomotor speed		
WAIS-R DSymbol[a]	11.0 (2.8)	4.3
TMTA[b]	0.30 (1.01)	4.3
Language		
COWA[c]	58.29 (27.91)	2.9
Learning and memory		
HVLT T1–3[b]	−1.01 (1.28)	37.7[a]
Executive function		
TMTB[b]	−0.51 (2.11)	21.7[d]
Motor[b]		
GPD[b]	−0.87 (1.36)	21.7[d]
GPND[b]	−0.61 (1.00)	13.0

SD indicates standard deviation from the mean. See Table 1 for test names and their abbreviations.

[a] Scaled Scores (mean of 10, SD of 3).

[b] *z*-scores (mean of 0, SD of 1).

[c] Percentile.

[d] Binomial test $P < .0001$.

Table 3.

Significant Correlations Between Predictors and Cognitive Marker Variables

	Significant Predictors				
Cognitive Tests	**Age**	**Years of Education**	**CESD**	**STAIS**	**AFP**
Attention					
WAIS-R DSpan	0.29[a]	0.47[b]	—	—	—
Psychomotor speed					
WAIS-R DSymbol	—	0.62[b]	0.37[b]	—	—
TMTA	—	0.27[a]	—	—	0.25[a]
Learning and memory					
HVLT T1–3	—	0.37[b]	0.28[a]	0.29[a]	—
Language					
COWA	—	—	—	—	—
Executive function					
TMTB	0.25[a]	0.52[b]	0.32[b]	—	—
Motor					
GRIP (dominant)	—	—	—	—	—
GRIP (nondominant)	—	0.26[a]	—	—	—

See Table 1 for test names and their abbreviations.

Metric: CESD (raw score); STAIS (standard deviation); Cognitive Tests (standardized scores)

[a]Pearson correlation $P < .05$.

[b]Pearson correlation $P < .01$.