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Cognitive problems in patients on androgen deprivation therapy: A qualitative pilot study☆

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Abstract

Objectives—Androgen deprivation therapy (ADT; also known as hormone therapy) is a well-established treatment for prostate cancer patients with rising prostate-specific antigen levels after localized treatment, and for those with metastatic disease. The neurological impact of ADT has been likened to that of aging and is therefore theorized to impair cognitive functioning in prostate cancer patients. We briefly summarize the research that has examined cognitive functioning of ADT patients primarily through neuropsychological assessment. A qualitative pilot study is presented with the aim of describing ADT patients' experiences of cognitive changes since starting ADT.

Materials and methods—Semistructured telephone interviews were undertaken with 11 community-dwelling prostate cancer patients undergoing ADT following definitive localized treatment. Participants were recruited via online prostate cancer support forums. Content analyses were conducted to establish relevant themes, which in this case were the cognitive domains of impairment.

Results—Eight of the 11 participants reported impairments in the domains of concentration, information processing, verbal fluency, visual information processing/visuospatial function, memory, and executive dysfunction. Neurobehavioral problems, including neurofatigue and apathy were also reported.

Conclusions—The interviews illustrate the potential negative effects of ADT on cognitive and neurobehavioral functions, and their impact on patients' work and in their daily lives. We describe how the field of cognitive rehabilitation offers promising tools to assist ADT patients with cognitive problems.

Keywords

Prostate cancer; Oncology; Cognitive function; Rehabilitation; Neuropsychology; Androgen deprivation therapy; Neurobehavioral function

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1. Introduction

Androgen deprivation therapy (ADT; also known as hormone therapy) is a well-established treatment for prostate cancer patients with rising prostate-specific antigen levels after localized treatment and for those with metastatic disease [1]. ADT has been linked by some researchers to impairments in cognitive functioning [2], and its neurological impact has been likened to that of the aging process [3]. In animals, androgen deprivation parallels the neuropathologic changes of aging; in humans, testosterone loss is associated with aging [4,5] and low testosterone levels are a risk factor for Alzheimer's disease [3]. Since ADT lowers testosterone levels, this is theorized to impair cognitive functioning in ADT patients [3]. Research has shown some support for this assertion (see reviews by Nelson et al. [2] and Jamadar et al. [6]), though studies have been limited by small samples or have not sufficiently examined risk factors that would determine who might be vulnerable to cognitive impairment. In this paper we (1) summarize the research, (2) highlight through a pilot study the need for in-depth qualitative investigations of ADT patients' experiences, and (3) describe how the field of cognitive rehabilitation offers promising tools to assist ADT patients with cognitive problems.

Two systematic reviews have been conducted to evaluate studies that used neuropsychological tests to examine cognitive effects of hormone therapy in prostate cancer patients [2,6]. Although Nelson and colleagues' [2] review noted inconsistent evidence for cognitive impairment following ADT, 47%–69% of ADT patients declined in at least 1 cognitive domain (over time periods ranging between 3 and 9 months) with visuospatial functions (i.e., spatial perception, mental rotation, and spatial visualization skills [7]) and executive functions (i.e., planning, inhibition, mental flexibility [8]) most commonly affected. Subsequent studies also reported variable results [9]. One reported declines in spatial reasoning, spatial abilities, and visual working memory during ADT that resolved after its cessation [9], but another found no statistically significant differences in individual test means between ADT patients and a healthy comparison group [10]. However, 42% of the ADT patients in the latter study displayed overall impairment (i.e., impaired performance on 2 or more tests) compared with 19% of the control group. Mohile and colleagues [11] noted declines in executive function among 38% of their patients from start of ADT to 6 months, whereas 48% improved in visuospatial function, though practice effects may have affected the measurement of visuospatial function. In exploratory analyses, the same authors found that when overall impairment was examined, those who began with impaired function tended to show no change in performance, whereas those with normal scores at baseline improved in some domains, suggesting that only unimpaired individuals benefited from practice effects and learning. In an effort to improve upon the small sample sizes in earlier studies, Alibhai and colleagues [12] evaluated a larger sample of prostate cancer patients starting continuous ADT ($n = 77$), and compared them with prostate cancer patients not receiving ADT ($n = 82$) and healthy controls ($n = 82$). When the proportion of participants with significant cognitive change over time was compared with proportions in either control group, there were no significant differences between groups. Yet, in a more sensitive regression-based measurement of change, ADT users 12 months after baseline saw a decline on attention and visuospatial working memory tasks, and a lesser gain on a visuospatial ability task than either control group.

In sum, existing research suggests that there is a potential negative impact of ADT on visuospatial functioning (including memory), executive functioning, and possibly verbal memory. However, most of the studies suffer from limitations that prevent strong conclusions. Most used only 1 test to evaluate each cognitive domain, and few comprehensively evaluated the areas of function that have shown possible decrements (e.g.,

executive functioning and spatial memory). Moreover, studies have not examined risk factors that might predispose ADT patients to developing cognitive impairment and that have been found in other populations to be associated with greater cognitive impairment (e.g., lower cognitive reserve in breast cancer patients who had undergone chemotherapy [13], and medical comorbidities in early dementia [14]). Hence, while studies suggest that ADT may result in cognitive impairments, more large-scale studies are still required.

Although the aforementioned studies examined cognitive functioning in ADT patients using objective (i.e., neuropsychological test) approaches, few studies have used subjective (i.e., self-report) approaches. Joly and colleagues [15] compared nonmetastatic prostate cancer patients undergoing ADT with a healthy age-matched control group and found no differences in subjective cognitive function. Yet, Voerman, and colleagues noted that men on ADT for more than one year reported worse cognitive functioning than men who received ADT for less than a year [16]. Unfortunately, these studies used short screening questionnaires or questions extracted from quality of life measures that limited their ability to examine the full range of cognitive problems patients might have experienced. Although subjective and objective measures of cognitive functioning tend to be weakly correlated [15], subjective experiences of cognitive functioning in cancer patients are generally related to reduced quality of life [16,17]. Additionally, the relationship between objectively-assessed cognitive function and “in vivo” functional abilities is moderate [18], allowing a disconnect between test scores and demonstrated functional abilities. Hence, in-depth analyses of ADT patients’ subjective experiences are needed to capture the lived experience (i.e., their self-understanding) of cognitive impairments and their impact on daily life functioning. Such data would highlight which difficulties are experienced as most challenging and distressing and, hence, worthy of clinical and scientific attention and possibly intervention. Qualitative interviews form a solid basis to capture patients’ phenomenological experiences [19] and provide information that quantitative methodologies cannot access, or may complement quantitative research [20].

While evidence for objective cognitive impairment following ADT highlights the existence of potential problems for some patients, a pilot study was undertaken to describe patients’ experiences of cognitive changes since starting ADT using qualitative information not reflected in objective tests and questionnaires.

2. Materials and methods

Eleven community-dwelling prostate cancer patients undergoing ADT following definitive localized treatment were recruited via online prostate cancer support forums. Participant characteristics are shown in Table 1. Because some participants did not know their cancer stage, this information was not reported. Semistructured telephone interviews lasting on average 20 minutes were conducted with each participant [19]. Participants were asked the question “Have you noticed changes to your thinking, concentration, or memory since starting ADT?” Follow-up questions were formulated based on individual responses. For example, if the participant answered “Yes, I have memory problems,” the interviewer probed further, asking for instances of those changes and how those changes affected the person’s life. Interviews were recorded and transcribed by the first author. Using standard qualitative methodology [19], interviews were coded by the first author according to whether participants endorsed the first question, and content analyses were conducted to establish the themes, which in this case were domains of cognitive impairment. All study procedures were approved by the study site’s Institutional Review Board.

3. Results

Eight of the 11 participants reported impairments that included problems in multiple cognitive domains. Most reported problems in lower level cognitive functions (concentration [$n = 5$], information processing [$n = 5$], and visual/verbal memory [$n = 6$]). Three participants reported problems with visual information processing/visuospatial function and 1 reported problems with verbal fluency. Two participants reported problems with higher level executive functioning. Neurobehavioral problems (i.e., the behavioral signs and symptoms associated with neurological dysfunction) were reported by 5 participants in the form of neuro-fatigue (i.e., brain tiredness; $n = 3$) and adynamia (i.e., lack of initiation, apathy; $n = 3$). See Table 2 for the themes and representative quotations.

Although prostate cancer patients tend to be older and, thus, often retired, all participants who reported cognitive problems had worked immediately before ADT. Two of the 3 participants who noted no cognitive problems had retired before ADT. All participants who reported cognitive problems also noted functional problems at work that they attributed to their cognitive problems and resulted in the need to cut down time spent at work, change jobs, or stop work altogether. Performance declines were noted, such as taking longer to do things and struggling to sustain concentration on the job. One participant noted that he struggled to do his work as quickly as he used to, but doing less work made the problems less noticeable. Participants also noted problems with functioning outside of work, including needing to reread information online or in books more than they used to, getting lost on the subway, misplacing things like their keys, and forgetting people's names. Participants were not asked about whether they used compensatory strategies to cope with such difficulties, but 1 participant indicated that he needed to write things down or else he would forget information.

Participants' experiences of people noticing these cognitive changes were variable: 1 participant reported that loved ones noticed "huge" changes; another participant stated that some people (including his wife) noticed changes at home; 2 participants noted that only their spouse noticed changes, and 3 participants indicated that no one noticed changes. Interestingly, 1 individual who did not report cognitive changes since starting ADT attributed his cognitive difficulties to the aging process.

4. Discussion

Overall, the results illustrate ADT patients' experiences of changes to cognitive and neurobehavioral functions, including in areas not consistently found to be problematic when assessed with objective measures in other studies. Specifically, problems were reported in areas that have been found to be problematic in previous studies, including executive functioning, visuospatial functioning and verbal memory, but also in areas not consistently found to be affected in previous studies, including concentration, information processing, and verbal fluency. Neurobehavioral problems not previously studied were also reported in the areas of neurofatigue and adynamia. Furthermore, participants reported that these problems affected their work and home lives, highlighting the potential need for cognitive rehabilitation for these individuals.

The data from this pilot study can help health care practitioners and researchers become more aware of how cognitive issues might be verbalized by patients and what to listen for, before referring patients for a neurological evaluation and/or formal neuropsychological assessment.

4.1. Potential cognitive rehabilitation approaches for ADT patients

Intervention studies to specifically help ADT patients with cognitive impairments have not been published. However, there have been studies (albeit few) that have investigated interventions in other cancer populations, including breast cancer and hematopoietic stem cell transplant patients. Among them, 1 cognitive rehabilitation intervention has shown promise among adult cancer patients. Ferguson and colleagues [21] investigated the potential benefits of a cognitive-behavioral treatment in 29 breast cancer patients reporting memory and attention problems after chemotherapy. The intervention included education on memory and attention, self-awareness training, self-regulation, and cognitive compensatory strategies training. Self-reported cognitive function, neuropsychological test performance, and quality of life improved at post-treatment time points, though the authors noted that without a control condition, the results needed to be interpreted with caution.

Given that cognitive rehabilitation has been helpful for breast cancer survivors, it seems worthwhile to examine the cognitive rehabilitation literature for potential interventions that could be adapted for ADT patients. Cognitive rehabilitation is an evidence-based treatment commonly used to ameliorate or compensate for cognitive impairments in non-cancer populations [22,23]. Two main approaches are discussed in the literature: (1) the use of compensatory strategies to reduce the functional impact of cognitive impairments; and (2) restoration of basic cognitive functions usually through direct engagement of those skills through graded exercises [22,24].

Physical exercise may also lead to cognitive improvement as evidenced by a multidisciplinary literature documenting its beneficial effects in humans and animals [25,26]. According to http://clinicaltrials.gov, a number of studies are investigating its potential benefit in human cancer patients with cognitive impairments.

4.2. Pharmacologic treatments for ADT patients with cognitive impairments

Although a number of mechanisms of action have been proposed that might explain the cognitive disruptions evident in some ADT patients [2,6], only a few small-scale studies have examined the effects of pharmacologic treatments on cognitive functioning in ADT patients. These studies have investigated the potentially beneficial impact of estradiol (a second line hormonal therapy) upon cognitive functioning. One study found improvement in verbal memory performance in patients undergoing transdermal estradiol therapy (following completion of ADT), but not in an active ADT group nor in a healthy control group [27]. However, 2 other studies that compared estradiol treatment with placebo in active ADT patients found no evidence for cognitive benefit [28,29]. Until the mechanisms of action have been more clearly elucidated in ADT patients, research into other potential pharmacologic approaches is likely to be premature.

4.3. Limitations

The first limitation of this pilot study is its small sample size that may have limited the range of responses that were reported. A second limitation is that most of the sample was Caucasian, thus limiting generalization to other racial/ethnic groups. A third limitation is that only basic medical information was captured. Future studies would need to gather more detailed medical and sociodemographic information from the sample to be able to draw connections between participant responses and medical/sociodemographic characteristics. A fourth limitation is that it is unclear whether the impairments reported are due to ADT side effects, aging, or demand characteristics of the interview situation.

5. Conclusion and future directions

Although research examining cognitive issues in ADT patients is still in its early stages, this pilot study and earlier research suggest that a proportion of ADT patients may experience cognitive impairments. Furthermore, as ADT becomes increasingly common, the number of patients affected will increase. Therefore, the field would benefit from research that helps health care professionals distinguish between ADT-related cognitive changes and those related to age-related and other disease processes (e.g., mild cognitive impairment, dementia), especially since testosterone loss is associated with aging [4,5] and low testosterone levels are a risk factor for cognitive decline, specifically Alzheimer's disease [3]. In addition, evaluating how impaired cognitive functioning impacts a person's daily life will become increasingly important. Neuropsychological tests are not always good predictors of daily life functioning [18], yet the impact of cognitive impairments upon a person's "real world" function is important (e.g., ability to navigate in a car, remember conversations, continue to work, perform household chores) [30]. Studies that have used subjective approaches so far have only tapped into a small piece of these real world outcomes, indicating a need for more comprehensive measurement of the impact of cognitive impairments on daily life functioning in ADT patients. By extension, gathering information about how patients cope with or compensate for such difficulties would also be important.

Despite the fact that many patients may not experience cognitive impairment following ADT, those who do experience cognitive impairment would likely benefit from interventions. Due to similarities between the cognitive problems experienced by ADT patients and those experienced by older adults with mild cognitive impairment, rehabilitation approaches found to be helpful in that population may also be helpful for ADT patients. Adapting existing rehabilitation approaches to specifically help ADT patients with cognitive impairments and evaluating such approaches will be an important area of future research.

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Table 1

Participant characteristics ($n = 11$)

Characteristic	n	%	M	SD	Range
Age			59.45	8.80	42–69
Patient ethnicity					
Caucasian	9	81.8			
African American	1	9.1			
Arab	1	9.1			
Months since beginning ADT			45.95	36.91	10–140
Frequency of ADT					
Continuous	9	81.8			
Intermittent	2	18.2			

Table 2

Themes and representative quotes

Theme	Representative Quotes
Cognitive functions	
Concentration	—"My concentration is not as sharp as it was."
	—"(When my concentration) gets broken, it's hard to get back into things."
	—"The biggest thing is lack of concentration."
Information processing	—"I'm not as quick as I was. I'm not 100%."
	—"Things are slower at work."
	—"It takes me longer to do things. I'm not as efficient as I used to be."
Verbal fluency	—"I do notice myself missing words."
Visual information processing/ visuospatial function	—"I couldn't see the sign in my brain. I'd have trouble reading the sign."
	—"I used to notice things out of the corner of my eye when driving, but I'm not as sharp now."
Verbal memory	—"I'll be in conversation, then forget what I was going to say."
	—"I'll finish a story but then forget what the story was and go back and reread it."
Visual memory	—"I lose my keys about 3 times a day. I'm like my mother-in-law before she died."
	—"I would forget where I was going and why I was going where I was going."
Executive functioning	—"Sometimes I can't do things as well as I used to, so I will force myself to complete one thing before I move on to the next."
Neurobehavioral functions	
Neurofatigue	—"Intense concentration just wipes me out."
	—"… waking up in the morning feeling like a Mack truck just hit me."
	—"I was doing work for 2 hours in the morning, I was just wiped."
	—"I feel like my head is in a fog."
Adynamia	—"(ADT) makes me feel apathetic."
	—"It's hard to get motivated."
	—"My general drive has decreased, I lack application."