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Short Communication

Intravesical Bacille Calmette-Guerin (BCG) Vaccine Affects Cognition

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Abstract. The Montreal Cognitive Assessment (MoCA) is a valuable assessment of the patient's awareness of time and place. We show that bacille Calmette-Guerin (BCG) significantly affects MoCA testing when administered by the intravesical route. MoCA scores were lower with increasing age and higher in more formally educated individuals. Patients receiving BCG tended to maintain their MoCA scores, whereas almost half the control cases tended to show reduced scores. This benefit is supported by reduced pre-amyloid biomarkers in BCG-injected healthy volunteers and a favorable effect on neuronal dendritic development in animal models. Our results suggest that BCG has a beneficial impact on the cognitive status of older individuals.

Keywords: Alzheimer's disease, bacille Calmette-Guerin, cognition, Montreal Cognitive Assessment, vaccines

INTRODUCTION

Recently, several vaccines have been cited as lowering the risk of developing dementia [1–7]. Our studies and others have shown that intravesical bacille Calmette-Guerin (BCG) is significantly effective in treating non-invasive muscle superficial bladder cancer and correlates with less dementia in treated patients [1, 4]. In our Israeli institutions, as well as in four other independent medical centers, a reduction of dementia and, more specifically, Alzheimer's disease (AD) has been in the order of 80% to 19% following BCG treatment [1, 2–7]. Here, we have added an early monitor of cognition, the Montreal Cognitive Assessment (MoCA, https://mocacognition.com) [8] questionnaire to our bladder cancer patients to determine if BCG affects cognition. Early recognition of cognitive impairment would be preferable to awaiting diagnosis of full-fledged AD and may improve the success of an intervention.

MATERIALS AND METHODS

The MoCA test consists of 30 points administered to the patient in about ten minutes. The test measures "short-term memory, visuospatial abilities, executive functions, attention, concentration and working memory, language, and orientation to time and place" [8]. Patients attending the urology clinic with a history of bladder cancer were recruited for this prospective evaluation. After signing an informed consent, they filled out the MoCA questionnaire. The testing person was blind to whether the individual had received BCG. Correct answers to 26 questions is considered normal, whereas below 26, the indi-

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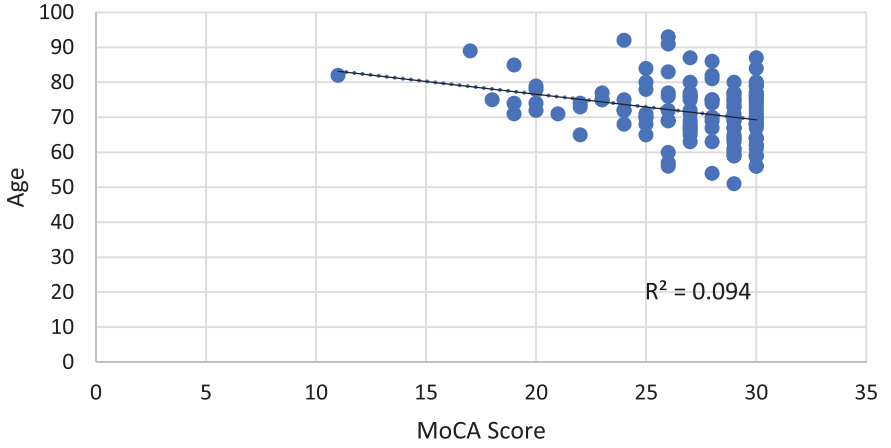

Fig. 1. Effect of age on MoCA scores.

vidual is deemed to have mild cognitive impairment (MCI). A total of 134 patients filled out the MoCA questionnaire at least once. Thirty-four patients performed the test twice; four were tested three times, one four times, and one five times. Almost three-quarters of the tests were repeated within 20 months, scheduled as closely as possible to being repeated within a year of the first test. The primary measurement was the change between the first and last MoCA measurements. A one-tailed Fisher's Exact Test was used to compare changes in the MoCA score of BCG receivers and non-receivers. The local IRB approved the trial.

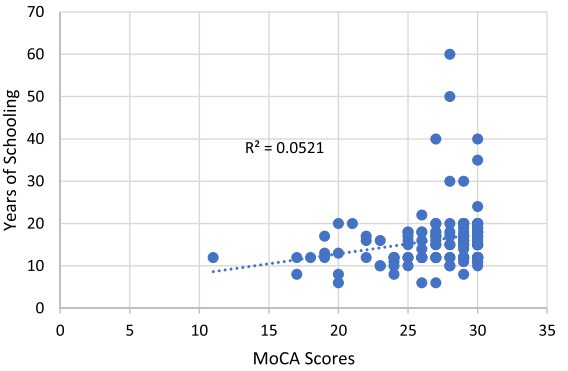

Fig. 2. Effect of schooling years on MoCA scores.

RESULTS

Population and the effects of age and schooling

The overall bladder cancer patient population gave a distribution of correct responses above 26 of 73%, with 27% in the area of MCI. Males predominated, with 83% ($n = 111$). The average age of the population was 71.4 years. Fifty-five percent ($n = 74$) were treated with BCG; of these, 11 (15%) were women, a ratio of 5.7 males to females, close to the national bladder cancer average of four males to each female [9]. The number of women treated with BCG was about half the total (11 of 23 – 47%). There was no difference in age between the patients receiving BCG and the controls (72 versus 71.4 years).

The first MoCA score versus age is plotted in Fig. 1, showing a trend to lower values with increasing age ($p = 0.0026$; the slope is defined as –0.122 MoCA answer scores per year of age). As illustrated in Fig. 2, years of schooling showed an upward MoCA score trend ($p = 0.0099$, with a slope of 0.11 per year of education). The very high values of school years were of Yeshiva scholars, who spent most of their lives in traditional Jewish studies.

MoCA retesting: the effect of BCG

Of the 34 MoCA-retested individuals, 20 received BCG, and 14 did not (controls). Both groups were predominantly males; those receiving BCG were 18 males and two females, and the controls were 12 males and two females. The average age of the retested individuals was 73 years, slightly above the general average. The average time between the first and second MoCA evaluations in the BCG and control groups was 15 and 20 months, respectively. The percentage of MCI-diagnosed patients did not change upon retesting; in both the first and second tests, it was 25% and 14% respectively. However, more than half of the 34 retested individuals moved upward (1–6

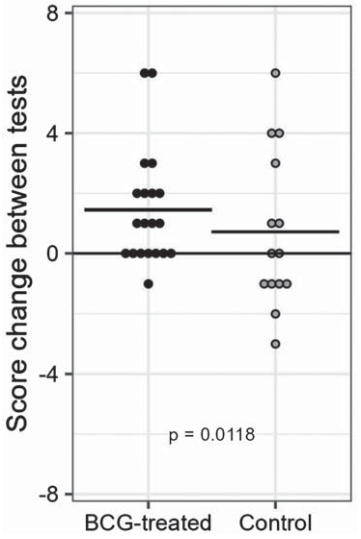

Fig. 3. Score change between tests in BCG-treated and control patients.

points or more per individual), and one-quarter stayed the same. This increase may have indicated a familiarity with the procedure. Of greater interest was that seven individuals moved downward.

We took advantage of the retesting to determine the effect of BCG on the MoCA score along a timeline. The median score of the first MoCA tests was the same for BCG-treated and control groups (median score 28). Figure 3 presents the change in MoCA scores between the first and the second tests in both groups. One individual immunized with BCG showed a minor decrease; the rest showed either exact repeats ($n = 7$) or an increased score ($n = 12$). Notably, six were recorded as lowering their MoCA score among the unvaccinated individuals, and only one in the BCG-treated group. We removed from these considerations two outliers: one in the BCG-treated group, with an increase of 12 points, and one in the controls, with a decrease of 13 points. A one-tailed Fisher's Exact Test for the two groups' equal negative results gives a p-value of 0.0118, significant at $p < 0.05$ but not at $p < 0.01$. Of the six control individuals whose scores were reduced, the clinical records showed that one was clinically diagnosed with MCI and was being treated.

DISCUSSION

Although the number of individuals is small, we believe this study is important for several reasons: 1) urological groups involved in similar research are relying on the dementia endpoint, while the MoCA test may provide insight into an earlier stage in the pathogenesis of AD, 2) several prospective studies applying BCG by injection are underway, with pre-amyloid tests being intermediate, but with AD as an outcome. Results will be years in coming unless changes in early cognition are accounted for, and 3) a pilot study of the robust biomarker of predictive of AD is a mass spectrometry-based plasma amyloid 42/40 ratio [10]. This, combined with age and *APOE*, can predict brain amyloid status. These parameters are incorporated in an Amyloid Probability Score (APS)—a score that identifies low, intermediate, or high risk of having cerebral amyloid. Results on forty-nine BCG-naïve, immunocompetent individuals nine months after vaccination found reduced risk assessment. Follow-up plasma amyloid testing revealed a reduction in the APS in all the risk groups, especially in the high-risk group of young individuals ($p = 0.016$). As we do here, the authors argued for skepticism in the "embracement of these results."

Metabolic studies of BCG support its role in affecting neuronal health. The studies of type 1 diabetes and BCG in activating trained innate immunity have all indicated that the monocyte/macrophage cell line shifts from anaerobic to aerobic glycolysis [11, 12]. Furthermore, it has been suggested that these cells, when passing through the blood-brain barrier, can transfer lactate to glial cells, which, in their cerebral role, can help to maintain neuronal health [12].

4) Three animal studies, with models for AD and Parkinson's disease [13, 15], have indicated a profound effect of BCG on the brain. Furthermore, one group reported a proliferation of neuronal dendrites [14].

In summary, this study suggests that BCG has a beneficial effect on the cognitive status of bladder cancer patients. In addition, the MoCA test may provide a valuable test for early AD diagnosis.

AUTHOR CONTRIBUTIONS

Charles Leonard Greenblatt, M.D. (Conceptualization; Formal analysis; Investigation; Writing – original draft); Herve Bercovier, D.V.M. (Conceptualization; Formal analysis); Benjamin Y Klein, M.D. (Formal analysis; Writing – review & editing); Ofer N. Gofrit, M.D., Ph.D. (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing – review & editing).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and in the table in its supplementary material.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-240307.

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