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BRIEF COMMUNICATION

Younger age is a good predictor of better executive function after surgery for pituitary adenoma in adults

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Abstract

Pituitary adenomas, even after successful treatment, are associated with cognitive dysfunctions. We hypothesized that an association between the age of the patients at pituitary surgery and neuropsychological outcome may exist. Forty-two patients (mean age 51 ± 10 years) who had been successfully treated for pituitary adenoma (surgery with or without subsequent radiotherapy) underwent neuropsychological testing. Age at treatment (mean 37 ± 11 years) was significantly associated with Trail Making Test, Part B (TMT-B) results, a measure of executive control and attention ($r = .60$, $p < .0001$). This association remained significant after adjustment for age at testing and time since treatment ($r = .42$, $p = .008$). No associations were detected between age at treatment and Trail Making Test, Part A (TMT-A, attentional speed), the digit span test (acoustic working memory), and the German version of the Auditory Verbal Learning and Memory, and Memory Test (verbal memory, all $p \geq .3$). Our data suggest a favorable effect of younger age at treatment in adults on neurocognitive outcome after surgery for pituitary adenoma. (*JINS*, 2009, *15*, 803–806.)

Keywords: Neuropsychological testing, Pituitary surgery, Prolactinoma, Cushing's disease, Acromegaly, Nonfunctioning adenoma

INTRODUCTION

Pituitary adenomas, even after successful treatment, are associated with cognitive dysfunctions (Peace et al., 1997). Impairments in memory and executive function have been reported by several studies (Grattan-Smith, Morris, Shores, Batchelor, & Sparks, 1992; Guinan, Lowy, Stanhope, Lewis, & Kopelman, 1998; Peace et al., 1997; Peace, Orme, Padayatty, Godfrey, & Belchetz, 1998). Many factors might contribute to these cognitive problems in patients diagnosed with and treated for pituitary adenoma, including mass effects from the original tumor on structures adjacent to the pituitary and hormonal imbalances. In light of the more severe impairments in surgically treated patients, the surgical procedure may be an additional contributing factor (Guinan et al., 1998; Peace et al., 1997, 1998). Although radiotherapy does not appear to impair cognitive function in patients treated for pituitary adenoma (Guinan et al., 1998; Peace et al., 1997, 1998), the impact of the kind of surgical route (transsphenoidal *vs.* transfrontal) is controversial in the literature. Peace et al. (1998) found more severe impairment after transfrontal than after transsphenoidal surgery, whereas Guinan et al. (1998) did not find an association between treatment invasiveness and the degree of cognitive impairment.

Several previous studies have shown that neuropsychological recovery after traumatic brain injury in adults was favorably moderated by younger age (Green et al., 2008; Testa et al., 2005; Willemse-van Son, Ribbers, Verhagen, & Stam, 2007; Wilson, 1998). Given that the influence of age at definitive treatment on cognitive function has, so far, not

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been investigated in patients surgically treated for pituitary adenoma, we aimed to test this association in the present study. We hypothesized that younger age at the time of treatment is associated with better neuropsychological outcome after successful intervention for pituitary adenoma.

METHODS

Participants

Participants were recruited from the endocrine outpatient clinics of the University Hospital of Tübingen. Inclusion criteria were successful definitive treatment for pituitary adenoma (pituitary surgery with or without subsequent radiotherapy), with no evidence of biochemical excess of growth hormone (GH), adrenocorticotrophic hormone (ACTH), prolactin, thyroid-stimulating hormone (TSH), or gonadotropins, and appropriate doses of hormone replacement as measured by endocrine tests on the day of neuropsychological testing. The length of time post-surgery ranged from 4 to 31 years [mean = 14 years, standard deviation (*SD*) = 8 years]. Thyroid, glucocorticoid, sex steroid, and growth hormone replacement therapies were considered adequate if free thyroxine (fT4) and free tri-iodothyronine (fT3) plasma levels were within the normal range, if the patient was receiving between 20 and 30 mg of hydrocortisone or between 25 and 37.5 mg of cortisone acetate per day, if plasma levels of testosterone or estradiol, respectively, were within the normal range, and if insulin-like growth factor-1 (IGF-1) levels were within the age-related normal range. Exclusion criteria comprised psychiatric and neurological disorders, major comorbidities known to affect neurocognitive function, such as liver abnormalities (alkaline phosphate, aspartate amino transferase, alanine amino transferase, or gamma glutamyl transferase levels 2 or more times the upper reference range), chronic renal failure (serum creatinine >1.5 mg/dl), marked anemia (Hb < 8.0 mg/dl), history of thyroid cancer requiring suppression of TSH secretion, visual deficits (an impairment in vision that, even with correction, adversely affects educational performance; i.e., a visual acuity of 20/70 or less in the better eye with best correction, or a visual field of 140 degrees or less in the better eye), and thyroid autoimmune diseases. The local ethics committee approved the protocol (protocol number: 249/2006V). Informed written consent was obtained from all participants.

Laboratory Methods for Hormone Concentrations

Cortisone-binding globulin (CBG), cortisol, estradiol, follicle-stimulating hormone (FSH), fT3, fT4, luteinizing hormone (LH), testosterone, and TSH were measured by an immunometric assay on the ADVIA Centaur analyser (Siemens Medical Solutions Diagnostics, Los Angeles, CA). ACTH, GH, insulin-like growth factor-1 (IGF-1), and sex hormone-binding globulin (SHBG) were measured by an immunometric assay on the Immulite 2500 analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA).

Neuropsychological Testing

Established and validated neuropsychological tests were utilized. Executive function was examined with the Trail – Making Test (TMT), which requires a subject to connect-the-dots of 25 consecutive targets on a sheet of paper. Two versions are available: A, in which the targets are all numbers (1, 2, 3, etc.), and B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). TMT-A examines attentional speed, and TMT-B is a measure of executive control and attention (Reitan, 1992).

Verbal memory was assessed with the German version of the Auditory Verbal Learning and Memory Test (VLMT), which consists of five presentations with recall of a 15-word list, one presentation of a second 15-word list (interference test), a sixth recall trial of the first word list, and a delayed recognition test after 30 min (Helmstaedter, Lendt, & Lux, 2001).

Acoustic working memory was assessed with the digit span test of the German version of the Wechsler Adult Intelligence Scale (WAIS) in which a subject is read a list of numbers and then asked to repeat it both forward and backward (Tewes, 1999).

Premorbid intelligence was estimated based on post-surgery administration of the Multiple Choice Word Fluency Test (MWT-B). It consists of 37 items requesting the individual to select the only meaningful term from among five options given for each item (Lehrl, 2005).

Below average performance was defined as a score above 39 s for TMT-A, above 85 s for TMT-B (Reitan, 1992), below 40 for VLMT (T-scores; Helmstaedter et al., 2001), and below 7 for the digit span test (age-related scores; Tewes, 1999).

Data Analysis

Ln-transformation of nonnormally distributed parameters was performed prior to statistical analysis. Distribution was tested for normality using the Shapiro-Wilk W test. To identify potential confounding variables, stepwise regression analysis was performed using a backward elimination approach. In multivariate linear regression analyses, neurocognitive performance was the dependent variable, whereas age at treatment, age at testing, and time since treatment were the independent variables. A p value <.05 was considered statistically significant. The statistical software package JMP 7.0 (SAS Institute, Cary, NC) was used.

RESULTS

Forty-two patients (17 males, 25 females) participated in this study. At the time of testing, the age of the patients ranged from 28 to 65 years (mean = 51 years, *SD* = 10 years). The age range at definitive treatment was 17 to 57 years (mean = 37 years, *SD* = 11 years). Participants had undergone trans-sphenoidal surgery for nonfunctioning adenoma in 6 cases, for prolactinoma in 11 cases, for acromegaly in 14 cases, and for Cushing's disease in 11 cases. The range of tumor size

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was 2 to 55 mm (mean = 17 mm, *SD* = 13 mm). In 12 participants, cure required two or more interventions, with 4 patients receiving a transfrontal approach. Radiotherapy was carried out in 18 cases.

All pituitary patients had normal estimated premorbid intelligence (IQ: mean = 106, *SD* = 13), as assessed by the MWT-B test. The pituitary adenoma group displayed attention and executive functioning deficits, as assessed by increased mean values of the TMT-A (mean = 42 s, *SD* = 19 s) and TMT-B (mean = 98 s, *SD* = 51 s) tests. Approximately half of the subjects showed results below the average in both tests. Although mean values of the VLMT (T-score: T1, mean = 49, *SD* = 9; T2, mean = 46, *SD* = 9; T3, mean = 45, *SD* = 9; T4, mean = 46, *SD* = 9) and digit span test (age-related score: mean = 11, *SD* = 3) were within the normal range, in the VLMT subtests, which assess verbal memory, up to one third of patients showed results below the average range.

We found a highly significant association between age at definitive treatment and results in TMT-B ($r = .60$, $p < .0001$). Participants diagnosed at a younger age showed better performance. Previous studies reported correlations among TMT performance with age, education, and gender (Drane, Yuspeh, Huthwaite, & Klingler, 2002; Heaton, Avitable, Grant, & Matthews, 1999). To identify potential confounding variables in our study, we performed a stepwise regression analysis, comprising age, gender, and education level, as well as other clinical factors, such as surgical route (transsphenoidal *vs.* transfrontal), number of surgeries, radiotherapy, tumor size, and time since treatment, which may influence neurocognitive function. The analysis showed that only age at testing and time since treatment independently contributed to predict TMT-B performance ($p = .0012$ and $p < .0001$, respectively), whereas the other factors did not influence results in TMT-B (all $p \geq .13$). Also after adjustment for age at testing and time since treatment, the association between age at definitive treatment and results in TMT-B remained significant ($r = .42$, $p = .008$; Figure 1a). In contrast, no associations were detected between age at definitive treatment and TMT-A, digit span test, and VLMT (all $p \geq .3$).

Since TMT-B scores reflect not only executive function but also attention, we computed TMT-B-A scores by subtracting TMT-A scores (indicating attentional speed) from TMT-B scores (indicating the more executive aspect of divided attention). In a multiple regression analysis, age at definitive treatment was associated with TMT-B-A, which represents in contrast to TMT-B executive functioning only, when controlling for the influence of age at testing and time since treatment ($r = .32$, $p = .04$; Figure 1b).

DISCUSSION

In accordance with previous studies (Guinan et al., 1998; Peace et al., 1997, 1998), we detected deficits in memory and executive function in patients treated surgically for pituitary adenoma. Moreover, our data show that executive function was significantly associated with age at treatment, and

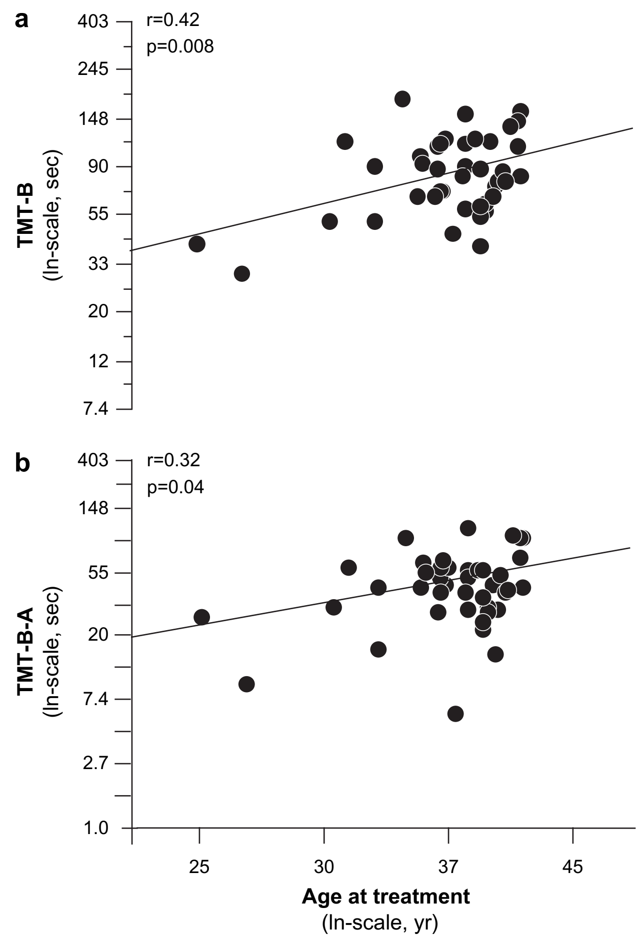

Fig. 1. Association of age at definitive treatment with executive function as assessed by (a) TMT-B scores and (b) TMT-B-A scores after successful surgery for pituitary adenoma. As TMT-B scores reflect not only executive function but also attention, we computed TMT-B-A scores by subtracting TMT-A scores (indicating attentional speed) from TMT-B scores (indicating the more executive aspect of divided attention). For statistical analysis, the data were ln-transformed and adjusted for age at testing and time since treatment. Sec = seconds; TMT = Trail –Making Test; yr = years.

that younger patients at definitive treatment exhibited a better outcome. This association remained significant after adjustment for the confounding variables age at testing and time since treatment and was independent of surgical route (transsphenoidal *vs.* transfrontal), the number of surgeries, radiotherapy, and tumor size.

Our results are in agreement with previous studies in adults indicating that a younger age at the time of insult is a favorable recovery factor after brain injury (Green et al., 2008; Testa et al., 2005; Willemse-van Son et al., 2007; Wilson, 1998). The reasons for the favorable effect of younger age in adults on neurocognitive outcome after traumatic brain injuries in previous studies and after surgery for pituitary adenoma in our study could be explained by two mechanisms.

The adult central nervous system possesses the life-long capacity for physical and functional changes enabling an

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effective cognitive rehabilitation after acquired brain injury. However, this neural plasticity declines with age (Burke & Barnes, 2006). Therefore, the decrease of neuroplasticity with age may be an explanation for the better outcome of cognitive functions following nonprogressive brain injury in younger adults. This assumption, however, is not supported by all studies (Reeder, Rosenthal, Lichtenberg, & Wood, 1996).

An alternative explanation for our finding may be the special vulnerability of elderly patients to neurologic disease and injury (Kulchycki & Edlow, 2006). In particular, the prefrontal cortex, the key brain area involved in executive function, shows considerable age-related neuronal loss and decline in white matter integrity (Burke & Barnes, 2006). The recuperative effects of younger age may, therefore, be attributable to greater reserve capacity of these brain areas.

The underlying mechanisms leading to an age-related decline of ability to recover from brain injury comprise a variety of factors, including region-specific changes in dendritic morphology, cellular connectivity, calcium dysregulation, gene expression, or other factors that alter neural network dynamics (Burke & Barnes, 2006). Furthermore, a growing body of evidence suggests that the GH/IGF-1 axis, which declines in parallel with cognitive function during aging, is involved in neuroprotection, regeneration, and functional plasticity in the adult brain (Sonntag, Ramsey, & Carter, 2005).

It is worth noting that we did not find an association between memory function and age at treatment. The reasons for the different influences of pituitary surgery on neurocognitive functions are not clear, and should be elucidated in future studies.

In conclusion, to the best of our knowledge, this is the first study reporting an association between age at surgery and executive function after successful treatment in patients with pituitary adenoma, with younger patients showing a better outcome. In future studies the underlying mechanisms should be carefully investigated.

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