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Clinical Study

Pre- and postoperative neurocognitive deficits in brain tumor patients assessed by a computer based screening test

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ABSTRACT

Neurocognitive assessment becomes increasingly important in neuro-oncology. The presence and degree of neurocognitive deficits in patients with brain tumors appear to be important not only as outcome measures but also in treatment planning and as possible prognostic markers for tumor-progression. Common screening methods for neurocognitive deficits are often insufficient in uncovering subtle changes or harbor the risk of being observer-dependent and time-consuming. We present data of brain tumor patients screened by a computer-based neurocognitive assessment tool before and after surgery. 196 patients with tumor resections were tested at our institution using the NeuroCog Fx® software 2 days before and 3–4 months after surgery. Additionally to the test results, patient-related information, such as age, sex, handedness, level of education, pre- and postoperative neurological status, KPS, location and histopathological diagnosis were recorded. These prospectively collected results were correlated in the here presented retrospective study. The majority of patients with malignant gliomas, metastases and meningiomas showed significant deficits in various neurocognitive domains, most of them improved or did not decline in their postoperative neurocognitive performances. Interestingly, there was no significant correlation of neurocognitive deficits and brain tumor location. In future, standardized neuropsychological assessment should become an essential part of the management and care of patients with brain tumors to provide a more personalized and tailored treatment. Further studies will improve the understanding of the influence of various treatment modalities on neuro-cognition.

1. Introduction

Brain tumors are heterogeneous diseases ranging from benign neoplasias, e.g. Meningioma WHO grade I, to very aggressive tumors like Glioblastoma WHO grade IV. Epileptic seizures, motor or sensory deficits, headaches, cranial nerve deficits or neuropsychological changes are possible initial symptoms. A neurosurgical intervention is usually the first crucial step in the treatment of brain tumor patients, at least to establish a histopathological diagnosis or to achieve tumor removal if it is safely possible. Tumor resection procedures are entailed by the risk to impinge on various functions of the brain, depending on the localization of the treated lesion. In addition to a surgical procedure, most brain tumor patients need adjuvant treatment like radio- and/or chemotherapy. The fact that possible side-effects of brain tumor specific therapies don't only affect simply measureable neurological functions like motor function but also more complex neurocognitive functions seems obvious and has become an important part of brain tumor research [4,6,16,20,22,31,32,37–40]. It is now well accepted that brain tumors and related treatments can impair cognitive functions. Not only neurocognitive deficits themselves, but also their possible predictive and prognostic value [18,24] and possible treatment strategies [10–12,22] have gained growing interest in the past. Especially in malignant brain tumors, a decline in neurocognitive functions may even be a measurable sign for tumor progression [2,23]. Although deficits in neuropsychological functions of brain tumor patients have been investigated in a number of studies, the latter predominantly provide cross-sectional data from already treated patients and there is very little focus on the influence of surgery on these deficits [27,29]. We therefore decided to perform prospective longitudinal assessments of individual neurocognitive functions in our setting of patient care.

In this retrospective study we share our initial experiences with the use of a computer-based neurocognitive screening tool. The

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test was implemented at our institution in 2009 and meanwhile it has been shown by Kerrigan et al. that screening for neurocognitive deficits in brain tumor patients is not only of scientific interest but might also prevent subjective misperception of the patients' mental capacity and thereby of their ability to provide informed consent [17].

Neuropsychological assessment is usually a time-consuming procedure that has to be carried out by specialized neuropsychologists and provides detailed information on various neuropsychological functions, e.g. language processing, memory, calculation or spatial orientation. Of course, not all of these functions may be of immediate clinical interest in the majority of brain tumor patients. This may contribute to the fact that testing for neuropsychological deficits mostly is not part of routine patient examination during brain tumor treatment. But, as shown before, these deficits seem to be of prognostic and predictive value and their revelation may contribute to an optimal treatment design [2,17,18]. Considering these facts, the department of Neurosurgery Graz has implemented a screening test battery for neurocognitive deficits in the routine pre-operative check-up and the first post-operative follow-up of patients with brain tumors requiring craniotomy procedures. Before the implementation of a neuropsychological screening tool, one has to make sure that the desired test is short (approx. 30 min.), repeatable, shows good psychometric properties (validity, reliability, and population norms) and is sensitive to changes in cognitive function, highly standardized and relatively simple to administer. It should also be completable by most patients, even those with considerable cognitive deficits, to avoid selection bias [22]. These features recommended by Meyers et al. in 2006 can be extended as proposed by Correa et al. in a review of 2007, which provided the basis for the development of NeuroCogFx®: [9] Assessment of cognitive domains sensitive to tumor and treatment effects, standardized training procedures and certification for individuals involved in test administration and availability in different languages [5]. In contrast to the Mini Mental State Examination [13,22,25], a dementia screening tool that is also widely used in brain tumor trials [3,33], we found that the neurocognitive screening software NeuroCogFX® meets the majority of these requirements to a high extent [8,9]. This software has originally been designed for neurocognitive screening in a variety of neurological disorders, especially epilepsy, at the Department of Epileptology, University of Bonn, Germany, and it has been standardized by testing 242 healthy individuals. Therefore, age standardization, critical differences to judge individual performances and an extensive assignment of subtests to neuropsychological domains are provided. Sensitivity and specificity for individual diagnosis of fractional neuropsychological dysfunction range from medium to high, but to a certain extent, training effects and only medium retest-reliability have to be taken into consideration for the interpretation of test results [8]. Recently, Fliessbach et al. have published data on practicability, retest reliability, practice effects, critical differences and validity for neurocognitive assessment with NeuroCogFx® in brain tumor patients enrolled in the German Glioma Network. In this study, the software was used parallel to a battery of established neuropsychological tests. Practicability was found to be good, retest reliability was medium-sized for most subtests in the control group (retest reliability $r_{1\ 2} = 0.5–0.7$) and brain tumor group ($r_{1\ 2} = 0.6–0.8$), but low in the 2-back test and simple reaction time in brain tumor patients ($r_{1\ 2} = 0.18$ and 0.33, respectively). Significant practice effects were seen in all subtests except the 2-back test and simple reaction time. These effects were not found when testing healthy individuals for a third or fourth time. The study revealed highly significant and strong correlations between NeuroCogFX® subtests and corresponding established tests (Pearson correlation $r = 0.43–0.80$). Regarding validity of the test, the authors were able to show in a factor analysis, that the software subtests represent 5 important cognitive domains, most of which are typically altered in brain tumor patients: (I) psychomotor speed, (II) attention/executive functions and visual working memory, (III) verbal memory and word fluency, (IV) verbal short-term memory and (V) figural memory. However, the factors attention/executive functions and visual working memory may be underrepresented [9].

Mean test duration is 25 min and the software design allows standardized, repeatable and simple application, in principle even by trained non-academic staff. With eight different subtests, the domains verbal short time memory, working memory, reaction time, selective attention, susceptibility to interference or cognitive flexibility, verbal learning and recognition, and phonemic-literal verbal fluency are assessed. We provide only a short summary of the tested neurocognitive domains in Table 1, as detailed descriptions of the test properties have been published previously [8,9,14].

2. Materials and methods

During routine preoperative checkup 1–2 days before undergoing craniotomy procedures and at their first postoperative follow-up exams after three to four months, a total of 196 patients (116 female, 80 male) with surgically treatable intracranial tumors underwent neurocognitive screening assessment using the NeuroCogFX® software. Patient's mean age was 56.6 ± 13.9 years, ranging from 18.6 to 80.3 years (f: 56.6 ± 14.4, m: 56.7 ± 13.2). All tests were performed from 2009 to 2012. Patients treated for pituitary adenomas were not included. All patients were informed that their test results will have no impact on their treatment plan. Testing was conducted by the two main authors (M.H. and L.B.) or occasionally by medical students under their supervision. Clinical data regarding handedness, focal neurologic deficits, seizures and Karnofsky Performance Status were stored in a prospective database. The histopathological diagnoses were categorized into 9 subgroups (Meningioma, High Grade Glioma [= HGG = Glioma WHO III and IV] and Low Grade Glioma [=LGG = Glioma WHO I and II], Metastasis, Vestibular Schwannoma, Hemangioblastoma, Lymphoma and Epidermoid Cyst). In order to provide comparable tumor location data, categorization into 15 subgroups was performed (Supratentorial: frontal, rolandic, parieto-occipital and temporal in left and right hemisphere; frontal midline-dominant lesions; Infratentorial: cerebello-pontine angle or hemispheres, midline cerebellar lesions and brainstem lesions). The NeuroCogFX® subtest results and total scores with percentile ranks were automatically saved by the software in text form. These were transferred to IBM SPSS Statistics (Release 20.0.0. 2011. Chicago (IL), USA: SPSS Inc., an IBM Company).

For interpretation of individual test results, the graduation system proposed by the test developers was used. Individual scores were given percentile ranks according to previously published normative data. Test results were categorized as follows: percentile rank (PR) = 0: very poor; PR < 3: poor; PR < 16: marginal; PR 16–84: normal; PR > 84: very good. The same classification was used for interpretation of subtests, overall score and overall test quality. The "overall score" of NeuroCogFX® is given in standard values, with a mean value of 100 and standard deviation of 10.

Categories were merged for group comparisons (frontal vs. other hemispheric, left vs. right hemisphere, left temporal vs. left frontal) and analysis of changes in pre- and postoperative test as "impaired" (marginal, poor or very poor, PR < 16) and "not impaired" (normal and very good, PR ⩾ 16). Either Chi-square Test or Fisher's exact Test were used for group comparisons. McNemar Test was used for analysis of changes between