Title

NCOG-14. NEUROCOGNITIVE FUNCTION AND QUALITY OF LIFE IN STABLE GRADE II AND III GLIOMA PATIENTS

Journal

Neuro-oncology, 19(Suppl 6)

ISSN

1522-8517

Authors

Luks, Tracy
Jakary, Angela
Chang, Susan
et al.

Publication Date

2017-11-01

Peer reviewed

Germany, [2]Department of Neuroradiology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, [3]Department of Neurology, Technical University of Munich (TUM), Munich, Germany, [4]Department of Neurosurgery, University of Mainz, Mainz, Germany

Though cognitive function is proven to be an independent predictor of survival in patients with intrinsic brain tumors, higher cognitive functions are still seldom studied. Aim of this study was to assess neurocognitive function and to identify risk factors for neurocognitive deficits in patients with intrinsic brain tumors. 103 patients with primary neuroepithelial tumors who received tumor resections or biopsies were included in this prospective study. The following data was acquired: mini-mental state examination, preoperative tumor volume, WHO grade, tumor entity and location, and the Karnofsky performance status scale. Furthermore, patients conducted an extensive neuropsychological testing battery of attentional, memory and executive functions. Regarding the results, general factors like age, clinical status, WHO grade, tumor volume and tumor location displayed a correlation with patients' neurocognitive functions. Affection of the parietal lobe resulted in significant impairment of attention and memory functions. Frontal lobe involvement significantly affected patients' abilities in planning complex actions and novel problem solving. Patients with temporal lesions were more likely to have impaired memory and executive functions. Comparing results among neuroepithelial tumor patients enables the identification of risk factors for cognitive impairment. General parameters such as age, KPS score, tumor size, and WHO grade are apart from the respective tumor location of high importance for patients neurocognitive function.

NCOG-11. COGNITIVE FUNCTIONS AND VARIANTS IN GENES ASSOCIATED WITH AGING AND INFLAMMATION IN BRAIN TUMOR PATIENTS

Denise Correa[1], Jaya Satagopan[1], Maria Kryza-Lacombe[2], Siok Leong[1], Sofia Dimitriadoy[1], Kelli O'Connell[1], Lisa DeAngelis[1] and Irene Orlow[1]; [1]Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]San Diego State University/University of California, San Diego, CA, USA

BACKGROUND: Cognitive dysfunction is common in patients with brain tumors treated with radiotherapy (RT) and chemotherapy (CT). We reported previously that single nucleotide polymorphisms (SNPs) in the *APOE*, *COMT* and *BDNF* genes may influence cognitive outcome in this clinical population. In this study, we assessed whether additional genes with known associations with aging, Alzheimer's disease and inflammation may contribute to cognitive dysfunction in brain tumor survivors. **METHODS:** One hundred and fifty patients with brain tumors participated in the study: ninety had been treated with RT ± CT, fifty-seven had CT alone, and three had no therapy. All patients completed neuropsychological tests of attention, executive functions and memory, and provided a blood sample for genotyping. We used a Bayesian penalized multivariate regression approach to estimate the associations between the SNPs and cognitive outcome, adjusting for age, education, tumor location, treatment with RT ± CT, time since treatment completion, and *APOE* epsilon e-4 allele. We quantified the strength of association between a SNP and a cognitive test score using a novel measure referred to as the posterior association summary (PAS) that takes value between 0 (= no association) and 1 (= very strong association). **RESULTS:** Several SNPs previously reported in association with age-related cognitive decline and Alzheimer's disease (*PDE7A* rs10808746, *CD2AP* rs9349407, *ABCC1* rs8187858, *APOE* rs405697) and inflammation (*IL-1A* rs1800587, *IL-1* rs1143634, *IL-6* rs1474348) were strongly associated with tests of attention, executive functions and memory (PAS ≥ 0.95). Several additional SNPs that mapped to the *ABCA7*, *CD33*, *COMT*, *IL-6*, *MS4A4E*, *PDE7A*, *PICALM*, *SERPINA3* and *SORC1* genes were also associated with tests of attention and executive functions with PAS ≥ 0.90. **CONCLUSION:** The findings provide new evidence that polymorphisms in genes associated with aging, Alzheimer's disease and inflammation may be functionally relevant and influence cognitive outcome in patients with brain tumors.

NCOG-12. NEUROCOGNITIVE OUTCOME IN CHILDREN WITH SENSORINEURAL HEARING LOSS FOLLOWING TREATMENT FOR MALIGNANT EMBRYONAL BRAIN TUMORS

Iska Moxon-Emre[1,2], Christine Dahl[1], Vijay Ramaswamy[1], Ute Bartels[1], Uri Tabori[1], Annie Huang[1], Sharon L. Cushing[1], Vicky Papaioannou[1], Normand Laperriere[3], Eric Bouffet[1] and Donald J. Mabbott[1]; [1]The Hospital for Sick Children, Toronto, ON, Canada, [2]Pediatric Oncology Group of Ontario, Toronto, ON, Canada, [3]Princess Margaret Cancer Centre, Toronto, ON, Canada

PURPOSE: Children treated for embryonal tumors are at risk for sensorineural hearing loss (SNHL). We report the prevalence of SNHL in children treated for malignant posterior fossa (PF) tumors and evaluate its impact on intellectual outcome, as a function of treatment. **METHODS:** Data from 104 survivors of malignant PF embryonal tumors, treated between 1996 and 2016 at The Hospital for Sick Children (Toronto, Canada) were included. Patients were treated with chemotherapy alone, or in combination with less radiation (reduced-dose radiation with a focal boost) or more radiation (treatments with higher radiation doses and/or larger boost volumes). All patients had audiological evaluations prior, during and following treatment, and 91 patients had 1 or more neuropsychological assessment. Growth curve analysis was used to determine stability or change in IQ scores over time. **RESULTS:** Severe SNHL was identified in 43 patients. Patients who developed SNHL had lower means than patients without SNHL on all IQ indices except processing speed (all $P < 0.05$). Patients with SNHL had lower intercepts for full scale IQ and verbal comprehension (all $P < 0.05$); however, all IQ indices declined by 0.9 points per year, regardless of SNHL (all $P < 0.05$). In patients treated with chemotherapy alone, those who developed SNHL had lower mean full scale IQ, perceptual reasoning and working memory than those who did not develop SNHL (all $P < 0.05$). In contrast, patients treated with radiation with and without SNHL did not differ in any IQ indices (all $P > 0.05$). **CONCLUSION:** Hearing loss is a much more significant complication than previously estimated in children treated for embryonal brain tumors. We demonstrate a profound impact of SNHL on intellectual functioning, in particular for patients treated with chemotherapy alone. Our results have implications for future trial design and follow-up for children with embryonal brain tumors.

NCOG-13. TOWARDS LONG-TERM MEMORY MAPPING DURING AWAKE CRANIOTOMY: VALIDATION OF A SHORT-FORMAT TASK IN PATIENTS WITH BRAIN TUMORS

Kelsey Bowman[1], Olivia Bjorkquist[2], Donna Bridge[3], Joel Voss[4] and Matthew Tate[5]; [1]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [2]Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [3]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [4]Departments of Medical Social Sciences, Neurology, and Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [5]Departments of Neurological Surgery and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

BACKGROUND: Patients with brain tumors often suffer from memory impairment, a symptom that results in a significant decrement to quality of life. However, unlike sensorimotor and language functions, memory is not mapped during awake craniotomies. Following on research showing that long-term memory processes are operative and can be measured over compact timescales, our goal is to develop a brief probe of memory function that will be suitable for the confines of the OR environment. Here, we report a validation study of a candidate task. **METHODS:** We designed a novel memory test in which patients studied collections of five objects arranged in a circle. After a 4s unfilled delay, the locations of two objects were swapped and patients attempted to identify these swaps. To vary difficulty, objects included either abstract squiggles or identifiable shapes. Fifty-five patients with supratentorial parenchymal tumors completed a series of standardized neuropsychological tests (including classical memory measures), as well our novel task. Neuropsychological battery performance was compared to performance on the novel paradigm using across-subject correlation analysis. **RESULTS:** 46/55 patients completed all components of the study. Performance on the squiggle version of the task was strongly correlated with total recall on the standardized battery ($r=0.586$, $p<0.0001$), whereas the object version correlated with a variety of domains, including total recall ($r=0.4267$, $p=0.0031$), visuospatial ($r=0.560$, $p<0.0001$), language ($r=0.485$, $p=0.0006$), and attention ($r=0.477$, $p=0.0008$). An analysis using moving averages across sequential trials indicated that only four squiggle trials were necessary to obtain a stable estimate of an individual's overall performance, and as low as a single trial for the objects. **CONCLUSION:** Our novel test provides a practical way to map both long-term memory (squiggles) and global cognition (objects) with low trial numbers, making intraoperative testing during awake craniotomy feasible, and may allow for more reliable preservation of cognition postoperatively.

NCOG-14. NEUROCOGNITIVE FUNCTION AND QUALITY OF LIFE IN STABLE GRADE II AND III GLIOMA PATIENTS

Tracy Luks[1], Angela Jakary[1], Susan Chang[2], Jennifer Clarke[2], Nicholas Butowski[2], Nancy Ann Oberheim-Bush[2], Sarah Nelson[1] and Jennie Taylor[2]; [1]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA, [2]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA

Neurocognitive function and quality of life are important clinical outcome measures for patients with lower grade glioma. Here, we performed neurocognitive testing and quality of life assessments in radiologically and clinically stable grade 2 and 3 glioma patients who are not receiving active treatment. **METHODS:** Patients completed a computerized battery of standardized neurocognitive tests in the NIH Toolbox and quality of life assess-

ments with the FACT-BR. We acquired patient demographic information, current performance status, current anti-epileptic therapy, treatment history, extent of resection at diagnosis and recurrence, tumor location, and histologic and molecular tumor characteristics. Tumor volumes were measured on T2 FLAIR MRIs. **RESULTS:** We have enrolled 15 patients. All patients had previous resection (10 partial, 5 gross total), 11 received chemotherapy, and 6 prior radiation. Median age at testing was 41 years old (range 26 – 65). As a group, patients were impaired on processing speed and fluid cognition. Two patients were impaired on picture vocabulary, 6 on list sorting, 11 on processing speed, 6 on sequence memory, 4 on inhibitory control, 2 on dimensional change, 7 on fluid cognition, and 0 on crystallized cognition. Higher age was significantly associated with poorer age-corrected oral-reading, and sequence memory. Insula and parietal lesions were associated with slower processing speed. Previous chemotherapy treatment was associated with poorer dimensional change. On imaging, larger tumor volumes were associated with poorer list sorting, processing speed, and sequence memory. On the FACT-BR, older patients, patients with prior radiation or those with higher grade were associated with poorer social/family well-being. **CONCLUSION:** The NIH Toolbox and FACT-BR are effective, accessible tools to assess neurocognitive function and quality of life in glioma patients. By correlating these assessments with patient and tumor characteristics, it may be possible to identify patients at risk for specific deficits and provide opportunity for intervention.

NCOG-15. LONG-TERM IMPACT OF RADIATION DOSE AND VOLUME ON INTELLECTUAL FUNCTIONING (IQ) FOR CHILDREN DIAGNOSED WITH MEDULLOBLASTOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Leanne Embry[1], Anthony Gioia[2], Yimei Li[3], Yunayuan Han[3], Patricia Cullen[4], Anna Janss[5], Jeff Michalski[6], Catherine Billups[3], Robert Noll[7] and Kristina Hardy[2]; [1]University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, [2]Children's National Health System, Washington, DC, USA, [3]St. Jude Children's Research Hospital, Memphis, TN, USA, [4]Regis University, Denver, CO, USA, [5]Emory University School of Medicine, Atlanta, GA, USA, [6]Department of Radiation Oncology, Washington University School of Medicine in St. Louis, St. Louis, MO, USA, [7]University of Pittsburgh Medical Center, Pittsburgh, PA, USA

OBJECTIVE: To examine longitudinal neuropsychological functioning in children receiving treatment for medulloblastoma on COG clinical trial ACNS0331. **METHODS:** Children aged 3 and older diagnosed with medulloblastoma participated in neuropsychological testing as part of the original study design or in conjunction with COG protocol ALTE07C1. Children under 8 were randomized to receive craniospinal irradiation (CSI) of either 18 Gy (reduced dose) or 23.4 Gy (standard dose); all children aged 8+ received 23.4 Gy. All children received either a 54 Gy boost to the entire posterior fossa (standard boost) or tumor bed (reduced volume boost), plus standard chemotherapy. Intellectual functioning (IQ) of children was evaluated an average of 0.67 (+0.21) and 2.99 (+0.59) years post-diagnosis. **RESULTS:** Of 464 eligible and evaluable patients enrolled on ACNS0331, 337 (72.6%) completed intellectual testing at one or both timepoints (mean age at diagnosis=9.1 [SD=4.06], range 3-19 years; 65.3% male; 83.1% white). Mean estimated IQ was in the average range at both timepoints (mean IQ T1=95.7 + 15.14; mean IQ T2=94.4 + 14.21), and declined an average of 2.2 (+ 9.98) points over time. Among children aged 3-7 at diagnosis, those randomized to standard dose CSI exhibited greater IQ declines over time than those in the lower-dose group (-7.2 vs. -0.4, respectively; p= .04). Among all ages, younger children (p <.01) and those who received a standard boost volume (p=.01) exhibited lower IQ at T2. **CONCLUSIONS:** Results of this prospective, randomized clinical trial suggest that children receiving a boost to the whole posterior fossa experience steeper declines in intellectual functioning over time. In addition, reducing whole-brain dose for younger children was also associated with less decline. Results suggest that strategies to limit the CSI dose and/or boost volume in children treated for medulloblastoma may improve neuropsychological outcomes. These approaches need to be weighed against the possible impact on disease control.

NCOG-16. A PILOT STUDY OF COGNITIVE FUNCTIONS, *APOE* AND AMYLOID IMAGING IN GLIOMA PATIENTS

Denise Correa[1], Maria Kryza-Lacombe[2], Xiaosun Zhou[1], Raymond Baser[1], Bradley Beattie[1], Zodina Beiene[1], John Humm[1], Lisa DeAngelis[1], Irene Orlow[1], Wolfgang Weber[1] and Joseph Osborne[1]; [1]Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]San Diego State University/ University of California, San Diego, CA, USA

BACKGROUND: Many patients with brain tumors treated with radiotherapy (RT) and chemotherapy develop cognitive dysfunction, and recent studies suggest that the Apolipoprotein E (APOE) ε-4 allele may influence cognitive outcome in cancer patients. The APOE ε-4 allele is known to promote deposition of beta (β) amyloid in the cortex, and preliminary evidence suggests that RT may be associated with this process. However, it is unknown whether β-amyloid accumulation may contribute to treatment-related neurotoxicity. In this pilot study, we assessed neuropsychological functions and β-amyloid retention using 18F-florbetaben PET in a subset of brain tumor patients who participated in our study of APOE polymorphisms and cognitive functions. **METHODS:** Twenty patients with gliomas treated with conformal RT ± chemotherapy participated in the study: 6 were APOE ε-4 carriers and 14 were non-ε-4 carriers. Patients completed a neuropsychological re-evaluation (mean time interval= 5 years, SD=0.83), and brain MRI and 18F-florbetaben PET scans. **RESULTS:** The results of Wilcoxon rank sums test comparisons between prior and current assessments showed a significant decline in selective attention (Brief Test of Attention, p=0.018), and a near significant decline in verbal learning (Hopkins Verbal learning Test-Learning, p=0.07). Comparisons by APOE status showed significant differences over time in attention and working memory (WAIS-III digits forward, p=0.028 & digits backward, p=0.032), with a decline among APOE ε-4 carriers. Comparisons of PET 18F-florbetaben regional standard uptake value ratios (SUVRs) showed near significance differences for the medial temporal cortex (p=0.069) and the putamen (p=0.069), with non-ε-4 carriers having higher SUVRs. **CONCLUSION:** The findings suggest that patients with gliomas may experience progressive worsening in attention and executive functions several years after treatment with conformal RT ± chemotherapy, and that the APOE ε-4 allele may modulate cognitive decline.

NCOG-17. COGNITION AND BRAIN STEREOTACTIC RADIOTHERAPY: A PILOT TRIAL

Emmanuelle Reygagne[1], Foucaud du Boisgueheneuc[2], Pierre Ingrand[3] and Antoine Berger[1]; [1]Radiotherapy Department, University Hospital La Milétrie, Poitiers, France, [2]Neurology Department, University Hospital La Milétrie, Poitiers, France, [3]Biostatistics Department, University Hospital La Milétrie, Poitiers, France

BACKGROUND: To evaluate a computerised cognitive test for the detection of information processing speed impairment in patients with radiation therapy for brain metastases named Interhemispheric transfer time test (IHTTT). **METHODS:** Medical inclusion criteria: patients≥18 years, with 1 to 4 brain metastases treated by stereotactic radiotherapy (SRT) with dose schedule: 33 Gy in 3 fractions, with a solid tumour, ≥70 Karnofsky Performance Status, with Mini-Mental State Evaluation (MMSE) ≥ 24, without medical history of stroke brain injury. 29 patients were recruited to our Center from June 2014 to April 2015. All recruited patients were administered a MMSE, the Frontal Assessment Battery at Bedside (FAB), a IHTTT and a quality of life questionnaire before SRT, and at one month, six months and one year follow up. The primary endpoint was Interhemispheric Transfer Time (IHTT). Secondary endpoints included IHTI (Interhemispheric Transfer Index), MMSE score, FAB score and quality of life. **RESULTS:** Our results suggest that IHTT and IHTI could detect a significant evolution of cognitive function over time (IHTT=720.3 ms ±26.5 at baseline, 728.0 ± 19.8 at one month follow up, 735.5 ± 36.1 at 6 month, 790.5 ± 109.1 at one year follow up, p=0.04, IHTI=13.1 ± 31.4, 11.5 ± 24.3, 50.6 ± 57.9, 82.2 ± 63.5, p=0.01). There is no significant evolution over time for MMSE and FAB score. This confirms their low sensitivity and specificity for detecting cognitive impairment. No significant evolution over time for quality of life questionnaire. **CONCLUSION:** IHTTT could be an interesting cognitive test to include in patients' evaluation with brain metastases irradiated by SRT.

NCOG-18. PHASE I TRIAL OF DIMETHYL FUMARATE, TEMOZOLOMIDE AND RADIATION THERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME: A PRELIMINARY NEUROCOGNITIVE PERSPECTIVE

Ashlee Loughan[1,2], Danielle Shafer[1], Autumn Lanoye[1], Sarah Braun[1], Paul Dent[1] and Mark Malkin[2]; [1]VCU Health / Massey Cancer Center, Richmond, VA, USA, [2]Division of Neuro-Oncology- Virginia Commonwealth University, Richmond, VA, USA

BACKGROUND: Cognitive deficits both prior to therapy and during treatment have been documented within the glioblastoma (GBM) population. As more effective therapies arise, the options to explore lasting cognitive effects broaden. Based on pre-clinical data demonstrating synergism with radiation (RT) and temozolomide (TMZ), a phase I study was conducted of dimethyl fumarate (DMF; provided by Biogen) in patients with newly diagnosed GBM in combination with standard therapy. To date, there is no documentation of neuropsychological correlates in the treatment of cancer patients undergoing this combination of therapy. **METHODS:** At the highest dose level, six newly diagnosed GBM patients received DMF 240 mg tid with RT (60Gy) and concurrent TMZ 75mg/m2, followed by adjuvant DMF and TMZ (150-200mg/m2 on days 1-5 of each 28 day cycle) for up to 6 maintenance cycles. Neuropsychological evaluations were performed across three time points (0, 3, 6 months). Repeated measure ANOVAs and