06-06
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Childhood Cancer Survivor Study (CCSS)

TITLE: Neuropsychological Status in Long-Term Survivors of Childhood Brain Tumors

WORKING GROUP AND INVESTIGATORS: This proposed study will be conducted in collaboration with the Neuropsychological/Psychosocial Working group of the CCSS. Proposed investigators include:

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PURPOSE: To evaluate neurocognitive functioning in a cohort of long-term survivors of childhood brain tumors by comparing them to surviviors of other types of cancer, a group of siblings and population norms; and to examine demographic, health status, and and treatment-related predictors of cognitive functioning in brain tumor survivors.

BACKGROUND AND RATIONALE:

Brain and central nervous system tumors, the most common solid tumors in childhood, are associated with a number of sequelae in adulthood including neurosensory, neurologic, neuroendocrine, social, psychological and neurocognitive.[1,2] In the neurocognitive domain, a decrease in global IQ measures compared to controls and normative samples has been reported as well as deficits in specific cognitive domains including verbal skills, visual spatial skills, executive function, attention, memory, psychomotor speed and learning.

A number of studies over the years have identified factors within the population of pediatric brain tumor patients that are associated with neurocognitive difficulties including tumor site,[3,4] age at diagnosis,[3,5] and radiation treatment[3,4,6]. In terms of site, cortical tumors are associated with more cognitive late effects than 3rd or 4th ventricle tumors. However, pediatric posterior fossa tumors have been associated with specific neuropsychological sequelae including deficits in attention, planning, sequencing, executive functioning, memory, processing speed, visual-spatial organization, modulation of affect and behavior.[7,8,9] This constellation of symptoms has been called the "cerebellar cognitive affective syndrome".[10,11]

Radiation therapy has been strongly implicated as a significant factor in the neurocognitive difficulties of brain tumor patients as well as of children with leukemia treated with prophylactic cranial radiation.[12] Correlation between the amount of radiation received and IQ declines have been repeatedly demonstrated.[13,14] Recent MRI studies suggest that radiation may result in damage to white matter including calcification and reduction in white matter volume that may account for these difficulties.[15]

Adult survivors of childhood brain tumors, as a group, show deficits compared to the general population as well as sibling and cancer control groups in IQ[6], educational attainment[1], income, employment[16], and marital status[1]. Survivors of ALL who were treated with cranial radiation also are at risk for lower IQ and educational attainment[17] when compared to ALL survivors who received no radiation therapy.[18] Several recent studies have attempted to assess the relationship between specific neuropsychological functions and the decline in IQ seen in individuals who received cranial radiation therapy for brain tumors or leukemia as children. Reddick et al found that deficits in attention but not memory correlated with decreased white matter and lower IQ in brain tumor patients[19]. However, working memory (the ability to hold information in mind for processing), but not processing speed was found to mediate IQ deficits in survivors of acute lymphoblastic leukemia (ALL).[20]

Executive Functions. A number of the specific neuropsychological functions found to be affected in individuals who survive posterior fossa tumors or cranial irradiation are part of the broader category of skills known collectively as the executive functions. The executive functions are viewed as a collection of related yet distinct abilities that provide for intentional, goal-directed, problem-solving action (Gioia et al., 2001). In Fuster's (1985, 1989) conceptualization, the executive functions are necessary for the organization of goal-directed behavior over a time dimension where cells within the prefrontal regions of the brain become activated for a sustained period of time during these cognitive activities, bridging the temporal delay between events. They are dependent on the integrity of the frontal lobes of the cerebral cortex and their widespread connections throughout the brain. Denckla (1994) defined the critical features of the executive functions for active problem-solving as follows: providing for delayed responding, future-oriented, strategic action selection, intentionality, anticipatory set, freedom from interference, and the ability to sequence behavioral outputs. Specific subdomains that make up this collection of regulatory or management functions include the ability to: initiate behavior, inhibit competing actions or stimuli, select relevant task goals, plan and organize a means to solve complex problems, shift problem-solving strategies flexibly when necessary, and monitor and evaluate behavior. The working memory capacity to hold information actively "on-line" in the service of problem-solving is also described within this domain of functioning (Pennington, Bennetto, McAleer and Roberts, 1996). Finally, the executive functions are not exclusive to cognition; emotional control is also relevant to effective problem-solving activity. The executive functions are crucial to many areas of life success as they underlie independent, self-directed behavior and problem-solving.

Deficits in executive functions are characteristic features in a variety of clinical disorders. For example, inhibitory control is a primary element of dysfunction in Attention-Deficit/ Hyperactivity Disorder (ADHD) (Barkley, 1997). Children with learning disabilities can vary in their ability to organize and plan long term tasks (Denckla, 1989). Problem solving rigidity has been associated with acquired brain injuries (Ylvisaker, Szerkeres, & Hartwick, 1992) and lead poisoning (Gioia, Guy & Isquith, 1997, Bellinger, Hu, Titlebaum & Needleman, 1994). Executive dysfunction has been reported in other disorders, including children treated for leukemia (Waber, Isquith., Kahn, Romero, Sallan,

& Tarbell, 1994), Tourette Syndrome (Denckla et al., 1991), psychiatric disorders (Rothenberger, 1992) and developmental disorders such as Pervasive Developmental Disorder (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995).

A widely studied population with executive function difficulty are children with traumatic brain injury (Ylvisaker, 1998). Problem-solving rigidity (Ylvisaker, Szekeres, & Hartwick, 1992), social interaction deficits (Eslinger 1997; Eslinger and Grattan, 1997), disinhibition, and planning deficits (Scheibel & Levin, 1997) have all been described in children who sustained traumatic brain injury. In this acquired neuropsychological disability, the greatest impact of executive deficits may not be seen in children at the time of injury, but emerge later with the dramatic increase of environmental, academic, behavioral, emotional and social demands on the executive system during adolescence and adulthood. Thus, acquired neurological disorders frequently result in deficits in executive function, which significantly impact the everyday functioning and quality of life of the individual.

Executive function has not been studied as extensively in another group of individuals with acquired neurological disorders, brain tumors, requiring more complete definition to better guide treatment planning. Yet, long-term survivors of childhood cancer, particularly brain tumors and leukemia, often have significant neurocognitive sequelae affecting their everyday adaptive functioning. Such sequelae may not be fully apparent until many years after treatment (Ris et al, 2001). It is important to determine the character and degree of sequelae, so patients on such studies can receive appropriate and timely intervention. For example, identifying the specific profile of neurocognitive deficits (e.g., poor working memory, disorganization), associated social-emotional factors (e.g., anxiety, and depressed mood), and dysfunction in tasks of community living enables concrete treatment targets that promote functional independence. Knowledge of the specific profiles of executive dysfunction are also essential for the development of the next generation of studies for survivors of childhood cancer.

Executive function can be a challenge to assess during neuropsychological evaluation because the structured nature of the clinical testing situation often reduces the need for executive skills. To more accurately evaluate deficits in the full range of components of executive functioning in children and adults, the Behavior Rating Inventory of Executive Function (BRIEF) was developed.[21] For school-age children, the BRIEF, a multidimensional standardized behavior rating inventory, is completed by a parent or teacher, whereas self-report versions are available for adolescents and adults (Guy, Isquith & Gioia, 2003; Roth, Isquith & Gioia, 2005). Studies indicate that the BRIEF is useful for differentiating normal children and adults from those with neurological disorders, expected to have deficits in executive functions (e.g. AD/HD).[22] Questions are asked which pertain to the following dimensions of executive functioning: Task initiation, working memory, planning and organization, task monitoring, response inhibition, mental flexibility and emotional control. An adapted 25-item version of the BRIEF, using those items that correlated the highest with the total scores of each of the BRIEF subscales, was developed and sent to participants in the CCSS study (see Appendix A).

Hypothesis

Within the brain tumor patients, it is hypothesized that health status, as well as treatment and demographic factors are correlated with executive functioning. The following analyses will be conducted:

1. Radiation.
    a. A dose-response relationship is hypothesized, with brain tumor patients receiving larger doses showing greater executive dysfunction. In addition, a site-related response is hypothesized, with those receiving cortical radiation having greater executive dysfunction than those receiving only sub-cortical radiation.
    b. Since leukemia patients also receive cranial radiation, an analysis which includes brain tumor patients and leukemia patients will be conducted to assess the dose-response relationship of whole brain radiation to executive dysfunction across a broader range of radiation doses.

2. Age at Diagnosis. Those who are younger at the time of diagnosis are expected to experience greater deficits in executive functioning than those who were older at the time of diagnosis (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000).

3. Post-diagnosis duration. Time since diagnosis is hypothesized to be associated with greater deficits in executive function.

4. Educational attainment. Lower educational attainment will be associated with greater executive dysfunction.

5. Exploratory analyses:

    a. The effects of gender and executive function in cancer survivors will be explored as evidence exists that girls may have more severe neurocognitive sequelae resulting from combined radiation and chemotherapy (Ris, Packer et al., 2001; Waber, Gioia, et al., 1990).

    b. The relationship of family socioeconomic status to deficits in executive functioning will be explored with the hypothesis of a small negative correlation (i.e., higher SES associated with fewer deficits).

    c. Chemotherapy. The effects of various chemotherapeutic agents used in treating brain tumor patients will be assessed.

These hypotheses will be tested using correlational models, specifically multiple regression models, with medical and treatment factors, and demographic variables serving as the predictor variables and regressed on BRIEF outcome scores.

Motor and sensory deficits will be examined as covariates/ effect modifiers.

Participants.

Three distinct groups will be participants in this study: CCSS patients, sibling controls, and BRIEF normative controls. Characteristics of the groups are listed below.

Group	N	Age – Mean	Age – Range	% male
CCSS Patients	7592	31.4	17-54	49.2
Sibling Control	379	33.5	15-54	47.2
BRIEF normative control	910	31.8	18-54	43.8

Data Analyses/ Methods of Statistical Analyses.

Preliminary analyses of BRIEF scores in the two control groups. To determine similarities and differences in the distribution of scores between the two control groups – BRIEF normative sample and non-affected sibling group - preliminary analyses will be conducted on the BRIEF scores, examining differences between the two groups on the Total and subscale scores.

To verify that survivors of childhood brain tumors show deficits in executive functioning compared to survivors of other childhood cancers, sibling controls, and the general population, diagnostic groups of childhood cancer survivors will be compared to a matched sibling group and age-matched sample from the BRIEF normative group on the BRIEF Total score and the subscales.

a. Initial data management: examination of data with respect to missing data/ variables with plan for imputation (per statistical center).
b. Descriptive statistics, including means and standard deviations, and median levels of BRIEF scores will be conducted to characterize the overall functional status for the groups.
c. Three primary types of analyses will be conducted: correlational, group differences, and casual modeling. Executive function via the BRIEF scores will serve as the outcome variable.
    1. Appropriate statistic procedures of group differences will be tested using a multivariate analysis of variance (MANOVA). Appropriate demographic variables will be examined directly to examine their influence as covariates in a MANCOVA.
    2. Multiple regression procedures will be utilized to examine the relationship of predictor variables and continuous outcome variables. Logistic regression methods will be used when the outcome variable is categorical (e.g., employed vs. unemployed status).
    3. Structural equation modeling, using the EQS procedure (Bentler, 1995), will be employed to examine the causal relationships between demographics, medical treatment variables, and executive function.

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