Commentary: Study of the Neurobehavioral Consequences of Childhood Cancer: Entering the Genomic Era?

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The outlook for children diagnosed with cancer has significantly improved and continued to change since the late 1960s. Due to advances in therapy and diagnosis, the focus of psychological research and service has progressively changed from death and dying to surviving and cure, as well as possible neurobehavioral late effects, which is addressed in the accompanying papers (Moore; Butler & Mulhern, this issue).

The first papers addressing neurobehavioral issues of survivors of pediatric cancer focused on childhood acute lymphoblastic leukemia (ALL) and reported quite contrasting results. In the first study, Soni, Marten, Pittner, Duenas, and Powazek (1975) found that survivors of childhood ALL who had received central nervous system (CNS) preventative treatment, including 2400 cGy of cranial radiation therapy (CRT), did not have cognitive/intellectual deficits compared with a matched disease control group and were functioning in the average range. In another investigation, which studied similarly treated children, it was found that the majority had evidence of computed tomography brain scan abnormalities such as cortical atrophy, intracerebral calcifications, and white matter translucency (Peylan-Ramu, Poplack, Pizzo, Adornato, & Di Chiro, 1978). Subsequent papers identified reliable intellectual deficits in long-term survivors of childhood ALL compared with siblings or a control group (Eiser, 1978; Meadows et al., 1981; Moss, Nannis, & Poplack, 1981). Although early on it was suggested that the etiology of the deficits seen in survivors of childhood ALL could be mostly psychosocial (Koocher & O’Malley, 1981), the biologic etiology of these effects is now well established. A number of studies have related the neurobehavioral deficits to brain imaging abnormalities (Brouwers, Riccardi, Fedio, & Poplack, 1985; Ciesielski et al., 1994). Secondly, in controlled clinical trials, children who received CNS preventative treatment that included CRT have been shown to have lower levels of neurobehavioral performance than children treated with CNS preventative therapy that did not include CRT (Brouwers, Moss, & Poplack, 1992; Waber, Bernstein, Kammerer, Tarbell, & Sallan, 1992). Subsequent studies also started to better characterize neuropsychological deficits and identify domains at higher risk for late effects (Anderson, Smibert, Ekert, & Godber, 1994; Brouwers, Riccardi, Poplack, & Fedio, 1984; Saykin, Ahles, & McDonald, 2003). An increasing interest in the neurobehavioral consequences of pediatric brain tumors in survivors started (Ellenberg, McComb, Siegel, & Stowe, 1987) when some of the typical neurotoxicities of therapy became better known, the prognosis for pediatric brain tumors improved, and the incidence of pediatric brain tumors increased. As noted in the accompanying papers, a lot of similarities in neurobehavioral profiles and their progression over time have been noted in children with brain tumors and ALL.

It is clear that numerous factors determine neurobehavioral outcome in survivors of childhood cancer. Conceptually, these factors can be subdivided into mediators and moderators (Baron & Kenny, 1986). Mediators are factors that specify how or by which mechanisms an effect occurs, while moderators are factors that affect the direction and/or strength of the relation between a mediator and an outcome variable but are not by themselves pathogenic. Whether factors are mediators or moderators has played an important role in the attribution of late effects in the past, as noted before. In the recent past, most research emphasis was on relating the neurobehavioral sequelae to biologic factors, with disease- and/or treatment-related factors as mediators, and gender, age at diagnosis, time since diagnosis, and age at testing as common moderators. Although the mediators of the sequelae for the various diseases may be very different, the factors that moderate outcome seem to be rather similar for all cases in which, as a consequence of
disease and/or treatment, there has been an insult to the developing brain. More recently, the contribution of environmental factors such as socioeconomic and family status (Yeates et al., 1997) as moderators of neurobehavioral outcome following brain insult has been increasingly recognized, as is also noted by Butler and Mulhern (this issue). The future use of more sophisticated theoretical and analytical frameworks based on the models provided by Baron and Kenny (1986) and the applications by Holmbeck (1997, 2002) will allow a more critical way of thinking about factors that affect outcome and about analytical approaches to evaluate the contributions of these factors to the neurobehavioral late effects seen in these children.

One of the continuing controversies in the natural history of late sequelae of cancer treatment remains over what causes the prolonged and continuing decline in neurocognitive functioning that is observed both in survivors of ALL (Jankovic, Brouwers, & Valsecchi, 1994) and in survivors of brain tumors (Copeland, deMoor, Moore, & Ater, 1999; Palmer et al., 2003). The question is whether at the basis of this decline is a biologic or a psychological process, or both. That is, has the treatment (or the disease) disrupted an elementary psychological process, such as aspects of attention, working memory, or learning, that are critical for further development and the acquisition of additional skills (Palmer et al., 2001; Schatz, Kramer, Ablin, & Matthay, 2000)? Or has the treatment initiated a physiological process that is ongoing and causes continued neuronal damage, such as is seen in the incidence of delayed microvascularizations following CRT (Riccardi, Brouwers, Di Chiro, & Poplack, 1985) or as is proposed in models of continued excitotoxicity (Kishi et al., 2003; Lipton & Rosenberg, 1994; Quinn & Kamen, 1996) and prolonged neural precursor cell dysfunction (Monje, Mizumatsu, Fike, & Palmer, 2002). Additional studies will be necessary to further elucidate the etiologies for this decline, which also has important implications for possible forms of therapy to alleviate neurobehavioral late effects. If the etiology is largely biologic, a greater emphasis may be placed on possible neuroprotective strategies (Drachman et al., 2002; Quinn et al., 1997) during or shortly after treatment. If the etiology is largely psychological, educational preventative strategies, initiated during therapy (Moore et al., 2000) or shortly thereafter (Anderson, Godber, Smibert, Weiskop, & Ekert, 2000), may be more effective and should be investigated, as is also noted by Butler and Mulhern (this issue).

Moore and Butler and Mulhern (this issue) also note that one of the observations that keeps on intriguing us is the vast amount of individual variation in outcome. Children with very similar prediagnosis neurobehavioral functioning and identical treatment may differ vastly in their outcomes. The factors that determine these individual differences are not well understood and, as is noted in the reviews, constitute one area that is likely to be a domain of much research in the future. I believe that particularly the further development of investigations of genetic polymorphisms will contribute significantly to a better understanding and possibly better individualized adjustment of treatment. I believe that there are two avenues of this research. The first is the investigation of polymorphisms that specifically affect the therapies that are given to the children. The second comprises polymorphisms or genetic factors that may make one more or less vulnerable to certain types of brain insult and thus to certain cancers and their treatments. For the first type, the polymorphisms with the broadest spectrum that affect the response to therapy are probably in the glutathione S-transferases (GSTs), which are part of a family that catalyzes detoxification of many chemotherapeutic agents as well as free radicals associated with radiation. A number of polymorphisms of these GSTs (GSTM1, GSTP1, and GSTT1) that can affect the clearing of the agents have been identified and associated with medical outcome (Stanulla, Schrappe, Brechlin, Zimmermann, & Welte, 2000), and may affect neurotoxicity. Furthermore, a number of genetic factors have been identified that affect the metabolism of specific chemotherapeutic agents (Whitehead et al., 1998). For example, methotrexate (MTX), an antifolate metabolite, is a major agent in cancer therapy. Its anticancer actions are through the depletion of folate, a building block necessary for cell replication. Common polymorphisms have been identified of methylene tetrahydrofolate reductase (MTHFR), a folate-metabolizing gene that results in a further decrease of folate levels in response to MTX and increased levels of homocysteine, an excitotoxin. The polymorphism (MTHFR-677-T) has been associated with better medical outcome and may be an important factor in late neurobehavioral effects (Kishi et al., 2003).

Similarly, genetic factors that make one especially vulnerable to radiation damage, also of the CNS, have been discovered. Some of these genes have well-recognized phenotypes, such as in ataxia-telangiectasia (Cunliff, Mann, Cameron, Roberts, & Ward, 1975; Hart, Kimler, Evans, & Park, 1987) and in Nijmegen breakage syndrome (Bakhshi et al., 2003). Others, such as the polymorphisms of the human x-ray cross-complementing groups 1 and 3 (XRCC1 and XRCC3) have less obvious phenotypes but have demonstrated a relation to normal tissue...
radiosensitivity (Andreassen, Alsner, Overgaard, & Overgaard, 2003), and preliminary data have shown a relation with neurocognitive outcome following radiation in adult patients with brain tumors (Wefel & Meyers, 2004). It is still likely that many other genetic factors and polymorphisms will be found that significantly affect the response of normal tissue to radiation, and thus influence outcome (Alsbeih, Story, Maor, Garea, & Brock, 2003).

There is an expanding literature addressing the second type of factor, polymorphisms or genes that may make one more or less vulnerable to certain types of brain insult or CNS-related manifestations. For example, the negative effects of the polymorphism of apolipoprotein E4 are well known in Alzheimer's disease and other neurologic outcomes following brain insult and may play a role in the neurobehavioral response to cancer therapy.

Also, it has been hypothesized that the etiology of adverse late neurobehavioral effects is associated with dysregulation of excitotoxic factors and cytokines/chemokines. Polymorphisms that affect the levels of cytokines and chemokines have been identified. For example, for the cytokine interleukin-10, which may have neuroprotective effects and is produced mainly by macrophages, an important component of the immune system within the CNS, a polymorphism has been found that affects survival outcome in human immunodeficiency virus (HIV) disease (Shin et al., 2000). Similarly, in children with HIV we demonstrated that polymorphisms that affect the levels of chemokines were associated with long-term neurobehavioral outcome (Sei et al., 2001). Little or no research has been conducted to investigate whether similar genetic factors also may play a role in the variance in neurobehavioral outcome seen in survivors of childhood cancer.

The development of new approaches to diagnosis and characterization, particularly of brain tumors, may provide a further opportunity for the study of genetic influence on neurobehavioral development. The data provided through chip technology from these studies using brain tissue will allow a further focus on the effects a growing tumor may have on its environment. For example, a number of studies have identified paraneoplastic effects in children, which are neurobehavioral abnormalities associated with cancers such as ALL and neuroblastoma that do not necessarily involve the CNS and occur prior to any treatment (Jankovic et al., 1989; Mitchell et al., 2002). The chip technology will provide data on either up- or downregulation of genes and gene products that also may be critical in normal neural development and be possibly associated with these manifestations. Some likely candidates are the tyrosine kinases (Trk), which are receptors for neurotrophins and other neural growth factors and are the subject of many studies in basic developmental neuroscience. For example, TrkC is a receptor for neurotrophin-3, which is critical for neural development. TrkC upregulation, however, also has been implicated in medulloblastoma and associated with better survival outcome (Grotzer et al., 2000; Pomeroy et al., 2002). Similarly, TrkB is the receptor for brain-derived neurotrophic factor (BDNF), which in the brain supports survival and process outgrowth of neurons. BDNF and TrkB have been associated with other solid tumors, such as neuroblastoma (Edsjo et al., 2003). Other new techniques, including proteomics (Lubec, Krapfenbauer, & Fountoulakis, 2003), may also provide data on proteins active within the CNS, such as reelin (Deguchi et al., 2003; Quattrocchi et al., 2003), that are critical in normal development of the CNS and have been found upregulated in certain CNS tumors. Hopefully, the data from some of these studies can be used to explain part of the variation in the neurobehavioral consequences of neoplasms both prior to and following treatment. These data may add a factor to those already used to explain the variance in neurobehavioral compromise prior to treatment, which so far has included the type of tumor, the location of the tumor, and the patient's age (Beebe & Holmes, 2002). Similarly, these data may factor in the explanation for the variation in the long-term response to the tumor and its treatments, particularly where it concerns neural plasticity and recovery of function.

The coming decades will most likely see a greater emphasis on studies applying more advanced forms of technology and analysis, with fewer patients studied more intensively, and a greater emphasis on the individual and individualized approaches. I think it will be a very exciting time, in which neuropsychologists can play a critical role.

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References


