Neurocognitive Late Effects in Children with Cancer

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Introduction

Families of children recently diagnosed with cancer may experience disruptions across multiple domains in their normal daily life and routine. Disruption in the child's cognitive and educational development during treatment for cancer has the potential to adversely impact quality of life well into the child's future. Fortunately, most children with cancer are able to successfully resume their premorbid cognitive and educational trajectories once their acute medical symptoms have resolved and their physical health has stabilized following completion of their cancer treatments.

However, there are subgroups of survivors who remain at risk for prolonged disruption as well as the development of new deficits in the years following completion of cancer therapies. Primarily, these are patients who have survived cancers involving the central nervous system (CNS) or who have received cancer therapy that can damage the developing brain, placing them at risk of developing long-term neurocognitive and behavioral sequelae. Survivors of acute lymphoblastic leukemia (ALL) and brain tumors, the two most common malignancies of childhood, are especially susceptible to these negative outcomes. Other groups that are relatively less studied but thought to be at risk due to the therapies received include patients who undergo stem cell transplantation, survivors of acute myelocytic leukemia (AML), and non-Hodgkin lymphoma (NHL), as some of these patients may receive intrathecal chemotherapy and/or total body irradiation depending on their disease status.

Research over the past three decades has helped us to identify some of the biological, clinical, and patient-related risk factors associated with neurocognitive impairment and has increased our understanding of the types of neurocognitive late effects that may be experienced

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A.N. Abrams et al. (eds.), *Pediatric Psychosocial Oncology: Textbook for Multidisciplinary Care*,
DOI 10.1007/978-3-319-21374-3_10

by childhood cancer survivors. More recently, these lines of research have led us to begin to evaluate potential prevention and intervention approaches to address these problems in the subpopulations most at risk. In this chapter, we present information on the disease, treatment, and patient-related factors relevant in understanding neurocognitive outcomes in high-risk survivors of childhood cancer. We also provide information on common areas of neurocognitive dysfunction, general considerations and clinical practice in the neuropsychological evaluation of children with cancer, and an overview of research investigating a variety of interventions and approaches to prevent or reduce neurocognitive dysfunction.

Disease and Treatment-Related Risk Factors

Children with Brain Tumors

Approximately 70 % of pediatric brain tumors are classified as malignant, typically requiring aggressive, CNS-directed therapy consisting of surgery, radiation, and chemotherapy, either alone or in some combination. Cranial radiation was the cornerstone of pediatric brain tumor therapy for many years and has contributed to a 5-year survival rate of about 66 % overall and 70–80 % for medulloblastoma (Imbach et al. 2006). Radiation therapy involves the delivery of high-intensity radiation beams to tumor sites and is most effective in tumors that are aggressive and have rapid cell division. Radiation therapy for CNS tumors may be delivered to the entire brain, to the entire brain and spinal axis, or to a focal area of the brain. In many cases, whole brain radiation is combined with an increased dose boost to the site of the tumor and sometimes to the area surrounding the tumor (e.g., the posterior fossa). However, as long-term survival was achieved, radiation to the brain was quickly identified as a major reason for the emergence of long-term neurocognitive deficits, ranging from declines in global intelligence to reduced functioning in specific neurocognitive processes (Packer et al. 1987). Cranial radiation is also associated with other late effects, such as neuroendocrine abnormalities and fatigue, which may further exacerbate lowered neurocognitive functioning (Schwartz et al. 2000).

Because of these adverse late effects, there are ongoing efforts to alter the intensity of treatment provided to children with CNS tumors. Specifically, protocols have attempted a more targeted approach where children with a relatively lower risk clinical profile (i.e., less aggressive disease) receive a reduced dose of radiation therapy, and radiation is substituted with chemotherapeutic agents for very young children (Baron et al. 2013). In contemporary treatment protocols for children with brain tumors, patients classified as high risk based on clinical characteristics continue to receive higher dose of cranial radiation while the dose to average-risk patients is lower. Recent prospective, longitudinal follow-up of children with medulloblastoma clearly shows a substantial difference in neurocognitive decline between children who received 23.4Gy of craniospinal irradiation compared to those who received 36–39.6Gy, with poorer outcomes in high-risk patients (Palmer et al. 2013).

Children with brain tumors frequently have a number of disease- and treatment-related factors which can adversely impact their neurocognitive functioning. These factors include the location and infiltration of the tumor in the brain, the presence or absence of hydrocephalus, and the postsurgical complications which may occur, such as posterior fossa syndrome. The most common neurosurgical complications are bleeding, which can result in hemiparesis, speech impairment, visual deficits, and a variety of motor and sensory impairments (Packer et al. 1987). While there typically is some recovery of functioning after an acute neurosurgical event due to brain plasticity, long-term disability may also occur.

Neurocognitive outcomes in children with brain tumors may also be further impacted by possible neurotoxicity due to chemotherapy. The chemotherapy agents most commonly used in the high-dose regimen for childhood brain tumors include cisplatin, cyclophosphamide, etoposide, methotrexate, thiotepa, carboplatin, and topotecan. The effects of chemotherapy in children treated without radiation has not been

well studied yet; however, preliminary findings suggest brain injury occurs even without cranial radiation, possibly due to a combination of tumor, surgery, and chemotherapy effects (Nelson et al. 2014).

Children with Leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and is the most frequently cited example of success following the advances in cancer treatment for children, with cure rates today of 80 % without relapse at 7–10 years after diagnosis (Imbach et al. 2006). However, earlier treatment regimens involving aggressive therapies that resulted in the improved survival rates were found to often occur at the expense of significant late effects in health outcomes, especially neurocognitive functioning.

As in the case of pediatric CNS tumor patients, there has been considerable literature documenting the adverse impact of cranial radiation therapy (CRT) on the cognitive outcomes of patients diagnosed with ALL. CRT is currently employed as a treatment procedure for ALL patients considered at high risk for relapse within the CNS (Moleski 2000). However, there appears to be a threshold of radiation intensity at which cognitive deficits are seen in patients with ALL, with evolving consensus that there are minimal cognitive late effects observed in most children who receive 1800 cGy or less, as their performances on cognitive tests are comparable to the normal population (Waber et al. 2007). Further, there is emerging evidence that proton radiation therapy may be associated with fewer cognitive deficits compared to traditional photon radiation therapy and this is an ongoing area of investigation in the effort to reduce risk for neurocognitive dysfunction (Pulsifer et al. 2010).

Given the known deleterious effects of CRT on neurocognitive function, CNS-directed chemotherapy has largely replaced CRT for patients diagnosed with ALL. Methotrexate (MTX), an antifolate, is an important component of all therapies for ALL. It is administered intrathecally to prevent leukemic involvement of the CNS and on a weekly oral schedule for 2–3 years as a component of virtually all maintenance therapies. MTX is also given intravenously, although the dose and schedule of infusion vary across treatment protocols and may include leucovorin rescue. There is ongoing research within the Children's Oncology Group to evaluate the cognitive and behavioral effects associated with these newer, potentially less neurotoxic treatment approaches (Noll et al. 2013). Results from these prospective, longitudinal studies will be helpful as the current published literature is mixed with respect to neurocognitive outcomes in ALL patients treated without radiation and only chemotherapy ranging from no effect of MTX to others identifying deficits in a wide range of neurocognitive processes (Buizer et al. 2009; Peterson et al. 2008). For the most part, findings suggest that IQ remains relatively intact; however, there may be subtle deficits in more specific neurocognitive functions, particularly attention and executive functioning processes (Buizer et al. 2009), as well as processing speed (Kahalley et al. 2013). Processing speed deficits can be particularly challenging, because children/teenagers have the cognitive capacity to do their work but are unable to complete it in a timely manner and this can lead to significant frustration and demoralization. There are no empirically validated treatments for slow processing speed.

More recently, Conklin and colleagues (2012) examined outcomes from the St. Jude Total Therapy Study XV which follows a protocol for induction therapy of intrathecal MTX for 13–25 treatments depending on risk status of the disease, as well as high-dose MTX given intravenously every other week for four cycles. The authors reported that while the ALL group was at significantly greater risk for sustained attention difficulties compared to a normative sample, no significant differences emerged for measures of intellectual functioning, academic skills, or memory (Conklin et al. 2012).

Discrepancies in findings about the impact of MTX on the cognitive outcomes of patients diagnosed with ALL may be related to the differences in the samples included in each study or may also reflect differences in the time since treatment. Time since treatment is an important predictor of neurocognitive outcomes, as longer time since

treatment is more consistently associated with impaired performance on neurocognitive assessment, as well as self-reports of poor cognitive and psychosocial functioning (Krull et al. 2013b). Although the mechanism by which neurotoxic chemotherapies such as MTX work on cognition is not entirely clear, there is some evidence of reduced cerebral white matter in the brain, in a similar fashion to CRT (Reddick et al. 2005).

Other CNS-directed systemic agents that have been used in the treatment of ALL include corticosteroid therapy. The type of steroid used (i.e., dexamethasone vs. prednisone) has not been found to have clinically meaningful differences on the cognition of ALL patients (Warris et al. 2014). However, it is difficult to assess the impact of these treatments alone since they are typically administered concurrently with MTX. Nevertheless, future research investigating the effect of CNS-directed systemic therapies on cognition, including corticosteroid therapy and high-dose MTX, is needed.

Hematopoietic Stem Cell Transplant

The research related to the cognitive outcomes of ALL patients who receive hematopoietic stem cell transplant (HSCT) is generally inconclusive. Some reports indicate no effect on cognition (Phipps et al. 2008), yet there is some evidence to suggest increased use of special education services in long-term survivors and decreased language skills relative to controls (Sanders et al. 2010). One retrospective study identified that children transplanted at a younger age and treated with CRT were found to have increased cognitive deficits (Smedler et al. 1990). In the largest, prospective, longitudinal study of children who underwent transplantation, Phipps et al. (2008) concluded that there may be some risk among those who received CRT but determined that this risk was not clinically significant. The difficulty in generating conclusive statements about the cognitive outcomes for HSCT patients is that many of these patients approach the transplant already immersed in intensive treatments and therefore, baseline assessments of functioning pre-transplant may not be an accurate reflection of premorbid function.

Lymphoma

Survivors of childhood cancers other than brain tumors and leukemia may also experience some neurocognitive late effects as a consequence of their cancer treatment. Similar to ALL, treatment for non-Hodgkin lymphoma (NHL) also involves intrathecal chemotherapies and survivors may have increased risk for neurocognitive deficits, especially if treated at a young age and with cranial radiation (von Der Weid 2008). Because of the biological and therapeutic similarities between ALL and NHL, many researchers have examined impact in these patients as a single group, and thus, there is relatively limited knowledge about neurocognitive outcomes in survivors of NHL. Self-reports of neurocognitive functioning from the Childhood Cancer Survivorship Study (CCSS) found that 13–21 % of adult survivors of childhood, non-CNS cancers had impairment on various aspects of executive functioning, when compared to a sibling cohort. In this sample, 9–18 % of NHL survivors placed in the impaired range on various executive function scales. Impaired executive functioning was also associated with lack of employment in this study (Kadan-Lottick et al. 2010). A recent publication documented significantly lower objective neurocognitive performance among long-term survivors of childhood Hodgkin lymphoma (HL) relative to national age-adjusted norms, as well as leukoencephalopathy in 53 % of the survivors (Krull et al. 2012). These results were attributed to delayed effects of cardiac and pulmonary toxicities from mantle field radiation; however, the study design did not permit examination in patients treated with chemotherapy only.

Neuroblastoma

Another compelling finding from the CCSS study is that hearing difficulty was associated with an increased risk in self-reported neurocognitive dysfunction (i.e., task efficiency, organization, and emotional regulation; Kadan-Lottick et al. 2010). The association between hearing and academic performance has also been established in otherwise healthy children but is only starting to gain

recognition among childhood cancer survivors. Gurney et al. (2007) studied 137 survivors of neuroblastoma and found that hearing loss was associated with learning problems and worse school functioning. Hearing loss is associated with chemotherapy such as cisplatin used to treat other malignancies; but interestingly with children with neuroblastoma, their neurocognitive deficits appear to be directly related to their hearing loss as opposed to other CNS-directed therapies.

Other Malignant Tumors of Childhood

Generally, survivors with soft tissue sarcoma, Ewing tumor, or Wilms tumor had self-reported neurocognitive functioning scores that were similar to or better than when compared with a sibling cohort (Kadan-Lottick et al. 2010). Survivors of osteosarcoma who receive IV methotrexate reported slightly poorer scores in task efficiency and emotional regulation when compared to siblings. It is unclear whether this difference is solely due to the effects of IV methotrexate or other aspects of their disease and treatment. Kadan-Lottick et al. (2010) reported that survivors who endorsed emotional distress, including anxiety and depression, were at elevated risk for impaired task efficiency, organization, memory, and emotional regulation.

Mechanisms of Neurocognitive Damage

Neurocognitive dysfunction secondary to CRT or chemotherapy results predominantly from cortical and subcortical white matter damage, with demyelination and glial cell destruction. Quantitative MRI studies in brain tumor patients have shown that the volume of normal-appearing white matter declines over time from the start of CRT and that this correlates with decreases in IQ. Additionally, CRT may disrupt the microvascular system supplying blood to the brain, resulting in calcification of fiber tracts and restriction of oxygen supply to portions of the brain (Kun 1997). Initially, radiation therapy was thought to cause acute, irreversible injury to normal tissues at the cellular level, leading to irreparable insults to organ function that remained stable over time. Currently, it is increasingly speculated that although radiation injures neurons, it is the response of multiple cell types to the radiation injury that creates chronic processes leading to progressive damage that continues over time (Wong and Van Der Kogel 2004).

Patient-Related Risk Factors for Neurocognitive Impairments

Neurocognitive late effects typically emerge within approximately 2 years following treatment completion. However, the degree of neurobehavioral deficit differs in magnitude based on a number of disease, treatment, and individual factors. Intensity of treatments and the age of the child at diagnosis and treatment are moderating factors, with younger age and higher treatment intensity associated with worse cognitive and behavioral outcomes. The interval between age at diagnosis and at time of cognitive assessment is also an important predictor with more severe deficits observed with longer time since treatment for some patient groups. At the same time, decline is also thought to eventually stabilize and may not be a linear process (Nathan et al. 2007).

The potential for adverse treatment-related neurocognitive impact appears to be associated with the degree of brain maturation at the time of therapy, with younger children being at great risk. Children with brain tumors who receive high-dose CRT prior to age four are at the greatest risk for severe, global neurocognitive deficits. For these survivors, graduation from high school outside of a specialized educational program is rare, and many are unlikely to be able to live independently as adults (Packer et al. 1987). However, for the majority of affected childhood cancer survivors, cognitive difficulties are to a less severe degree and affect discrete areas of cognition rather than having global impact. Many of these survivors are presumed to be able to compensate for specific cognitive weaknesses by employing targeted learning interventions, by utilizing environmental supports, and by relying

on areas of relative strength. Gender of the child and extent of resources (i.e., quality health care, optimal school and tutoring services, parent involvement, etc.) available to the child and family are additional predictors speculated as contributing to long-term outcomes but are not yet well studied (Patel et al. 2014a). Further, individual variation in neurocognitive outcomes following diagnosis and treatment for cancer may also be a result of genetic predispositions, such as polymorphisms in genes that modulate response to therapy or predispositions that influence response to physiologic stress and CNS integrity (Krull et al. 2013a). A list of the aforementioned factors that are thought to influence the nature and extent of neurocognitive impact experienced by children with cancer is presented below. See Box 10.1.

Box 10.1 Factors Contributing to Neurocognitive Outcome

Disease/treatment factors
Cranial radiation
Presence and location of a brain tumor
Surgical resection of a brain tumor
Chemotherapies known to be associated with neurotoxicity (neurocognitive, neuropathy, hearing loss, etc.) Methotrexate Vincristine Carboplatin/cisplatin
Type and severity of cancer (e.g., brain tumor, leukemia, etc.)
Modality and dose intensity (IV, IO, IT) Drug combinations such as with or without corticosteroids, leucovorin, cytarabine, asparaginase, etc.
Individual factors
Time since diagnosis/age at assessment
Age of child at disease onset
Gender
Pre-diagnosis functioning/precancer trajectory
Environmental factors (e.g., quality of school resources)
Genetic predisposition
Family functioning

Profile of Cognitive Impairment in Childhood Cancer Survivors

Common areas of dysfunction observed in survivors with a history of CRT and/or intrathecal chemotherapy include attention/concentration skills, processing speed, memory, visual-motor integration, and executive functions (e.g., planning and organizational skills, etc.) (Buizer et al. 2009; Robinson et al. 2010). Such abilities represent "core" mental processes by which children learn, store, organize and integrate, and effectively apply new knowledge and skills. In particular, changes in the underlying basic processes of attention and memory are associated with a lowered acquisition rate of new knowledge and skills relative to same age peers and, over time, impact the survivor's IQ and academic achievement (Palmer et al. 2001). Dysfunction in attention/concentration, processing speed, and executive function skills appear to be consistently reported in studies focused on neurocognitive impact in childhood cancer survivors and warrant special attention as they can initially be easily misinterpreted as volitional nonadherence by caregivers. See Box 10.2 for common manifestations in the child's daily life.

Box 10.2 Manifestations of Neurocognitive Dysfunction in Daily Life

Attention

- Trouble sustaining focus on a task over long periods of time and may lack awareness of these episodes of disrupted attention.
- Inattention may be overlooked or even mistaken for deliberate noncompliance.
- A tendency to miss bits of information when somebody is talking, especially if there is a lot of noise or commotion nearby.
  - May lead to inability to follow directions or understanding complex concepts.
- Careless errors, incomplete homework assignments, and inconsistent performance.

- May appear to have poor memory for things like schoolwork, but good memory for more personal things that are of greater interest.
- Negative social impact since kids do not notice when they are making mistakes, or doing or saying something wrong, but peers may notice.

Processing Speed
- Needs more time to finish tasks or to respond to a question
- Trouble keeping pace with the flow of instructions, demonstrations, and explanations

Working Memory
- Trouble attending to many different things or aspects of a problem at the same time
- Limitation on the ability to mentally "hold" information, instructions, or ideas in mind temporarily while performing other mental operations

Planning and Organizing Skills
- Trouble breaking down large projects into steps and figuring out the order in which to start
- Difficulty organizing time, as they do not know how much time to allow themselves to complete an assignment or job

Quality of Life Outcomes in Survivors with Neurocognitive Impairments

The impact of neurocognitive late effects on survivors of pediatric cancer is widespread and adult survivors of childhood cancer have been found to experience long-standing economic, psychological, and social consequences (Zebrack et al. 2004). Specifically, these survivors are more likely than their siblings to require special education services, less likely to attend college, and less likely to live independently as adults (Gurney et al. 2009). In addition, survivors of childhood cancer are at increased risk of unemployment compared to their siblings and are more likely to never marry (Gurney et al. 2009). See chapter 15 (survivorship) for more details.

Survivors of pediatric cancer, and particularly those with neurocognitive late effects, experience deficits in social adjustment (Schulte and Barrera 2010). Social adjustment has been defined as the extent to which individuals are achieving socially appropriate goals (Cavell 1990). These deficits worsen with time, affecting survivors' quality of life (Schulte and Barrera 2010). Research examining the relationship between neurocognitive processes and social adjustment is scarce in pediatric brain tumor survivors and has been identified as a gap in the literature. Typically, these constructs have been investigated independently. However, cognitive processes would be expected to have pervasive effects on a child's perception and interpretation of social situations and behavioral responses in social interactions. For example, children with cognitive-executive deficits may have difficulty thinking about multiple social perspectives or response options when determining how to respond to social stimuli. A link between attention dysfunction and social outcomes in survivors of childhood cancer has been reported (Moyer et al. 2012; Patel et al. 2007).

Considerations in Neuropsychological Evaluation of Children with Cancer

The field of pediatric neuropsychology has developed significantly over the years and the practice currently involves work with children and families in varied clinical settings, including children with cancer. In addition to the general qualifications for neuropsychology, providers who wish to practice in a pediatric oncology setting are encouraged to specifically pursue training opportunities under the direct

supervision of a licensed neuropsychologist experienced in the area.

From a research perspective, neurocognitive and behavioral assessments are valuable to conduct in conjunction with contemporary pediatric cancer therapies to examine differences between treatments which, in cases of similar medical outcomes, may ultimately determine treatment preference. From a clinical perspective, monitoring of neuropsychological functioning in children at risk for neurocognitive impairments is valuable to provide the medical team and the child's family with information relevant to the child's health status, particularly with respect to the emergence of late effects across time. Importantly, information from comprehensive assessments can be used to identify any delayed sequelae and to develop a plan of care for remediation of cognitive impairments. Results from the initial neuropsychological assessment are particularly helpful in guiding the course, timing, and plan of action for the child's transition back to academic and social environments. Subsequent assessments are helpful in tracking developmental progress, or lack of, in neuropsychological functioning. Results may also assist the family and medical team in understanding "problematic" behaviors. For example, identification of attention or memory problems may explain child's "nonadherence" in remembering to take medications or identify emerging problems that may impact daily living skills, such as effectively managing time to complete school assignments or activities of daily living. Ongoing monitoring of the child's neuropsychological functioning is also helpful to keep the family and medical team informed of changes across time, such as the emergence of new deficits or worsening of previously identified dysfunction.

Timing of Assessments

In general, a baseline neuropsychological evaluation is recommended following completion of primary treatments and after acute symptoms have resolved. Typically, this coincides with the child's transition back to the school environment. The Children's Oncology Task Force on Neurocognitive/Behavioral Complications after Childhood Cancer provided an expansion on the Children's Oncology Group's (COG) Long-Term Follow-Up Guidelines that offer direction on the timing of neuropsychological evaluation in pediatric cancer populations. According to these guidelines, survivors of childhood cancer should receive a baseline evaluation as they enter long-term follow-up (approximately 1–2 years post treatment), should be monitored annually for educational and vocational progress in the long-term survivorship follow-up program, and should be referred for periodic comprehensive neuropsychological reevaluations as clinically indicated (www.survivorshipguidelines.org). Typically, it is appropriate to reevaluate the patient during educational milestones and developmental transitional points (e.g., elementary to middle school, middle school to high school, and high school to college, etc.) and always when there are concerns of worsening functioning (Nathan et al. 2007). Unfortunately, not all centers have survivorship programs or staffing to provide repeated neuropsychological evaluations. Further, difficulties in securing insurance reimbursement for the neuropsychological evaluations, if done, can pose an operational barrier in providing an optimal level of care.

As described previously, children with brain tumors and ALL are at greatest risk for cognitive impairment, but the recommendation for regular monitoring of educational and vocational progress extends to children of any cancer diagnosis or treatment history. Prolonged school absences are common in children undergoing treatment for cancer which can negatively impact the child's ability to maintain pace academically; therefore, monitoring of learning and school-related difficulties would be appropriate in these cases as well. Neuropsychological evaluations can be helpful for children in this group as well, particularly for those who are struggling at school. Please see Chap. 11 (education) for more details.

General Clinical Practices in Neuropsychological Evaluation

One of the initial steps in neuropsychological assessment is a thorough review of records, which requires sifting through all the layers of information contained in medical records which may or may not be fully relevant to the case at hand. A review of neuroimaging reports (e.g., MRI, CT scans, etc.) is helpful in formulating the approach to neuropsychological evaluation, particularly in patients with brain tumor or CNS complications, given that the particular type of neuroanatomical involvement influences decisions about the battery of tests to administer. Further, in pediatric oncology specifically, it is important to gather records about the onset and associated history of the particular cancer diagnosis, as clinical-, disease-, and treatment-related factors are known to confer varying degrees of risk for cognitive and behavioral dysfunction. Also, information regarding the patient's specific treatment protocol is crucial in helping to attribute the various etiologies for any impairments that are identified as a result of the neuropsychological evaluation. In pediatric assessments, review of school records is essential to understand the patient's educational exposure and to correlate any academic and behavioral difficulties with neuropsychological performances. This process may include requesting previous educational plan documentation (e.g., Individualized Education Program), progress reports, report cards, or documentation from other providers in the school setting (e.g., school psychologist).

The clinical interview is another key aspect of neuropsychological assessment and the detailed information obtained using this procedure frequently facilitates conceptualization and hypothesis generation with respect to the child's struggles and how they manifest in daily functioning. The interview process frequently provides nuanced information regarding the severity, duration, or frequency of cognitive and behavioral symptoms that is typically not available in medical records. Incorporating details from collateral interview of parents, caregivers, teachers, other providers (e.g., therapists), etc., is also essential toward a comprehensive understanding of the child's struggles and how these are manifested in daily life. By the end of the clinical interview, the interviewer has gathered and clarified details regarding the patient's history across various domains (e.g., medical, developmental, family, psychosocial, educational, psychiatric, etc.).

Following the clinical interview, the pediatric neuropsychologist finalizes the specific tests to administer related to the neurocognitive functions of interest. When a comprehensive assessment is indicated, evaluation typically includes the following cognitive domains: academic achievement, attention/concentration, working memory, processing speed, language/verbal reasoning, verbal and visual learning and memory, executive functioning, daily behavioral and adaptive functioning, sensory, and gross and/or fine motor skills. As previously mentioned, particular domains known to be at risk for impairment in pediatric oncology populations should be the focus including global intellectual functioning, attention, executive functioning, processing speed, and nonverbal/visuospatial reasoning. Aspects of the neurological examination may also be administered based on the patient's level of direct neuroanatomical involvement or sensory presentation (e.g., visual field defect secondary to tumor resection). In addition to cognitive functioning, neuropsychologists evaluate psychological, behavioral, adaptive, and personality characteristics of their patients as well as how they integrate with the patient's neurocognitive presentation. Although generally less common in pediatric cancer populations, symptom validity testing may also be employed to provide information regarding the examinee's level of motivation or effort during the testing process (AACN 2007).

Screening Approaches

Comprehensive neuropsychological evaluations for patients at high risk for neuropsychological

impairments following cancer diagnosis and treatment are the gold standard but may not always be feasible given the practical challenges that arise in the current health-care setting. As noted earlier, comprehensive neuropsychological evaluations can be quite costly and are not always covered by insurance. In addition, full assessments can take a long time (e.g., 5 or more hours), and this is not always practical for families or within the time constraints of the clinic setting. Additionally, there may not be sufficient staffing to provide timely services to all children at high risk. In contrast, routine screening could become a fiscally responsible strategy used to target patients who are in need of more comprehensive evaluation (Krull et al. 2008b). Neurocognitive screening may range from a detailed interview to assess the child's school, social, and learning development to administration of brief, standardized neurocognitive measures, depending on the child's risk level. Given this context, a number of screening approaches are being evaluated (Embry et al. 2012; Krull et al. 2008a).

Regardless of whether a comprehensive or brief neurocognitive screening approach is used, test administration, scoring, and interpretation of test data are often considered the "core" components of a neuropsychological assessment and each has its standards and competencies characteristic of the process. However, with each step, it is important to consider not just the *test scores* but the larger context that provides the framework for the quantitative "data." For example, in an adolescent patient preparing for their senior year, what effect could recent news of relapse have had on the testing results? The patient could potentially become depressed and these symptoms might influence how scores from some or all of the neurocognitive tests are interpreted.

Feedback

There is evidence that parents of children with cancer have a strong interest and need for information about the impact of treatment on their child's neurocognitive functioning, both during treatment and in the years following its completion. Therefore, feedback and discussion of findings from the neuropsychological evaluation with the family are very important and frequently are dynamic processes (Trask et al. 2009). Feedback with patients and their parents in a pediatric oncology setting is typically provided in a separate face-to face session after the testing is complete, allowing clinicians to be in dialogue with parents about the assessment and recommendations.

Feedback from neuropsychological testing may at times take on a therapeutic tone during which the neuropsychologist aligns with the family in communicating the results. Feedback itself is more than simply reporting the patient's test scores and implications of the findings, and it should also be a comprehensive clinical interaction that helps a family or patient understand their child or themselves perhaps from a new perspective. The family's reaction and adjustment to the results provided are important to address, particularly as research suggests that parents have increased stress in managing and parenting children with higher cognitive dysfunction relative to those with more minimal neurocognitive impact (Patel et al. 2013).

Postal and Armstrong (2013) note that through the feedback session, patients and families have the opportunity to more deeply understand their diagnoses, testing scores, and expected prognosis. They also suggest that through the process of providing feedback, neuropsychologists assist patients' understanding of particular neurocognitive syndromes in the broader real-world context. The neuropsychologist may be the first provider to integrate the patient's medical and personal history, academic or vocational difficulties, and assessment results and conceptualize these pieces to tell a more complete story. During these sessions, it is not uncommon for additional information to arise or for the neuropsychologist to receive further clarification on an existing issue. In some cases, the written report may be finalized after these details are integrated into the documentation.

In addition to verbal feedback, a written neuropsychological report is the primary vehicle for summarizing and communicating the results of the evaluation to patients and their families. It serves as a reference for families in the future as a document of their children's strengths and weaknesses, including impairments, and may be a tool for advocating for their child's needs. Please see Education in Chap. 11 for details

about services that parents can advocate for. Therefore, it is especially important to understand that the language and professional "jargon" used in a report can be a barrier to a families' ability to interpret the results and should be used sparingly or avoided when possible. This can be the case even when parents have a university-level education (Cheung et al. 2014).

Feedback to the referring physician and the medical team involved in caring for the child is also necessary. It is important to help the team understand the child's functioning level for various reasons, ranging from feedback about the side effects experienced as a result of the treatment protocols used to preparing providers for the possibility of inconsistent treatment adherence due to forgetfulness or disorganization or even to help the provider tailor their communications to the "developmental age" and capacity of the child. Although this multidisciplinary feedback may take place in different formats across various work settings, it is often communicated in regular team meetings or more informal one-on-one conversations. Again, the written evaluation report becomes important as a communication tool with the medical team. There is not one "typical" style of a written report; length, amount of detail, and comprehensive nature of the report will vary. It is important, however, that reports include a summary and interpretation of results, address the referral question, and provide recommendations with relevant "next steps."

Finally, feedback provided to the school from the neuropsychological evaluation is essential. The recommendations and interventions formulated from the assessment can provide the scaffolding from which a more extensive and comprehensive educational plan can be devised. The unique insights provided from the evaluation often support a plan that is tailored to the specific needs of a student, often in the form of a 504 Accommodation Plan or Individualized Education Plan (IEP). Please see Chap. 11 on Education for more details. The plan is often best developed within the context of open communication between the family, school staff, and school administration. Without this open communication, procuring the appropriate services for children with cancer can be challenging because schools are often unaware of the specific disease-related neurocognitive and academic-related impairments experienced by this patient group. A case example of a childhood cancer survivor seen for clinical neuropsychological evaluation is presented below, as well as samples of questions typically asked in the neuropsychological interview.

Case Vignette

A right-handed, 22-year-old Hispanic and Caucasian male diagnosed at 16 years old with non-Hodgkin lymphoma of the bone and marrow is referred for a neuropsychological reevaluation by the survivorship clinic given concerns regarding his cognitive functioning and recommendations for college. The patient reported difficulties with executive functioning skills (i.e., sequencing tasks, working memory), maintaining attention, and processing speed. Memorization was also a new area of difficulty for him. These cognitive impairments were causing conflict with family members. The patient also reported significant anxious symptoms that presented physiologically (e.g., pain in his chest). He utilized spiritual coping (e.g., prayer) to manage his emotions. He reportedly drank socially but denied use of tobacco or other drugs.

He was born at 38 weeks' gestation with no reported pre- or perinatal complications. Developmental history was notable for a diagnosis of congenital hypotonia resulting in delayed motor skills. Speech and language developed normally. Medical history was also notable for a heart murmur and visual tracking difficulties. The patient was diagnosed with attention deficit hyperactivity disorder, inattentive type, as a child.

The patient underwent 8 months of treatment including cyclophosphamide, vincristine, prednisone, triple intrathecal therapy (methotrexate, hydrocortisone, cytarabine), and intrathecal systemic chemotherapy with cytarabine and etoposide. He was taking multivitamins, calcium, and an over-the-counter medication for attention problems, but no prescribed medications.

Box 10.3 Sample Questions Asked in the Clinical Interview

General clinical interview	*Question examples*
Purpose of the evaluation	Do you understand why your child's oncologist referred them for a neuropsychological evaluation?
Presenting cognitive complaints	Do you have specific concerns about your child's learning or thinking skills? Can you clarify the specific challenges your child is having? When did these concerns begin or when were they first brought to your attention? Have the difficulties worsened over time or stayed at about the same level? Have others noticed these challenges as well (e.g., teachers, other family members, caregivers)? Is there anything that seems to help your child in minimizing or managing these difficulties?
Neuropsychological domain	*Question examples*
Academic	Has there been a significant decline in your child's grades or performance at school? Is there difficulty in a particular subject area (e.g., reading, math)?
Attention	Is your child easily distracted or have difficulties focusing on the task at hand? Does your child require frequent repetition of instructions to complete a task correctly?
Executive functioning	Is your child routinely disorganized (e.g., lose or misplace personal items on a regular basis)? Does your child routinely turn in assignments late or wait to the last minute to complete them?
Processing Speed	Does it take your child longer than expected to respond to an instruction? Is your child routinely one of the last students to complete in-class assignments?
Visuospatial	Does your child find highly spatial activities (e.g., puzzles) difficult to complete independently? Are math concepts (e.g., geometry) particularly difficult for your child?
Language	Does your child exhibit challenges in expressing themselves verbally? Does your child seem to frequently have difficulty understanding what you ask them to do?
Memory	Does your child have difficulty remembering recent events? Does your child seem to forget details of recent conversations?

Family medical history was notable for chronic myelogenous leukemia, Parkinson's disease, diabetes type II, prostate cancer, multiple sclerosis, and coronary heart disease. Family mental health history was notable for severe depression, obsessive-compulsive disorder, and bipolar disorder.

Neuropsychological assessment included a clinical interview with the patient, collateral interview with the patient's mother completed with the patient's consent, one five-hour testing session, and feedback session. The patient required several breaks to maintain focus and he demonstrated occasional lapses in attention during the assessment. The results were considered to be a valid representation of his cognitive functioning approximately 5 years after completing treatment for non-Hodgkin lymphoma. He exhibited impairments in processing speed, sustained attention, and executive functioning (working memory, planning/organization, metacognition). He also evidenced a clinically elevated level of anxious symptoms and adaptive functioning

impairments related to educational difficulties and parental conflict. The cognitive impairments significantly interfered with the patient's ability to acquire new information and greatly impacted his learning efficiency.

As a result of the evaluation, specific recommendations were crafted to meet the patient's educational needs in the college setting. He partnered with the office for students with disabilities at his institution for support with implementing the accommodations and interventions. Consultation for ADHD medication was also recommended for the patient at the time of the assessment given his long-standing history of attention difficulties potentially exacerbated by his previous cancer treatment.

Interventions to Prevent or Reduce Neurocognitive Late Effects

Interventions for neurocognitive late effects of pediatric cancer treatment include educational interventions, targeted cognitive remediation, pharmacologic therapy, and behavioral interventions. Educational interventions include school remediation/reentry programs, cognitive behavioral therapy, training in social skills or specific subjects, and use of computerized cognitive training. Provider and family advocacy is essential to access educational resources such as IEPs or classroom and testing accommodations (i.e., 504 plans) as part of school reintegration for survivors of childhood cancer. School reintegration programs vary widely across the USA and by clinical site. Hospital-based programs have largely been more comprehensive and have replaced workshops for peers and educators (Castellino et al. 2014). The proposed standard for school reintegration is staged programs organized by a counselor-liaison to advocate for and interpret neuropsychological evaluations and to coordinate resources in the community, home, and hospital (Nazem and Butler 2011). Please see Chap. 11 on Education for additional details.

Cognitive Remediation

Child-Directed, Clinic-Based Approach

Cognitive remediation therapy in children typically includes interventions that use metacognitive training in problem-solving and managing complex tasks through individualized self-monitoring of effectiveness followed by self-correction (Hardy et al. 2011). Evidence supports the beneficial effects of cognitive remediation in children after traumatic brain injury or stroke (Catroopa et al. 2009). Because of the similarities between cognitive deficits in traumatic brain injury and those observed in cancer-associated cognitive dysfunction, cognitive remediation therapy has been investigated in childhood survivors (Anderson and Catroppa 2005). A feasibility trial in survivors and caregivers showed statistically significant improvement in focused attention but not in arithmetic computation (Butler and Copeland 2002). A follow-up, multicenter randomized trial demonstrated a statistically significant improvement in academic achievement in the cognitive remediation therapy group following a 5-month intervention, compared with controls randomized to a wait list (Butler et al. 2008). Results are tempered by an equivalent improvement in neurocognitive functioning in the control arm, attributed to practice effect. Further, only 60 % of the children in the intervention group completed the prescribed treatment, and the beneficial effects were not sustained long term. A shorter, 15-session, clinic-based intervention with long-term survivors also showed benefits but reported low participation rates, attributed to the demands placed on parents to bring the child to the clinic while managing other responsibilities (Patel et al. 2009).

Following the earlier focus on remediating dysfunction in long-term survivors, a pilot study was conducted to explore if early intervention might prevent math declines in children with ALL. Children on therapy for ALL were randomized to intensive individualized training in math problem-solving or to standard care. While the standard care group had higher scores in applied mathematics at baseline, the intervention group

improved such that it performed significantly better in applied mathematics and visual memory at the end of intervention and at 6-month follow-up. The standard care group did not improve in any area and declined in seven of 11 domains, illustrating the typical pattern of cognitive decline. Results from the pilot study demonstrated that early intervention is feasible and beneficial (Moore et al. 2012).

Computerized Training Approach

While clinic-based cognitive remediation has shown benefit in research studies, it is variably covered by insurance as a clinical service; hence, out-of-pocket cost limits access and in-person interventions may not be practical or desirable for families. Within this context, computerized cognitive training and remediation has been viewed as a highly desirable avenue to deliver intervention for cognitive deficits and has been studied in both brain-injured populations and, more recently, in childhood cancer survivors. Pilot trials of home-based, computerized brain training (e.g., Cogmed and Lumos Labs cognitive exercises) have demonstrated improvement in selected neurocognitive functions such as attention, memory, and visual processing skills, with some studies showing benefits from the parental perspective also, but without generalization to academic performance (Hardy et al. 2013; Kesler et al. 2011). More recently, a pilot computerized training program (Fast ForWord) to prevent reading delays was implemented while children with brain tumors were still undergoing therapy. The study demonstrated feasibility for prophylactic intervention but did not find significant differences in reading between the randomized groups (Palmer et al. 2014). A randomized trial of a home-based computerized training program targeting neurocognitive function is currently in evaluation as a feasibility study in childhood brain tumor patients following cranial radiation (NCT01503086).

Parent-Directed Approach

Given the limitations of clinic-based interventions directed at the child, a parent-directed intervention has been examined with the intent to indirectly benefit the child's learning and educational performance. Children of parents who received the eight-session skills training program showed significant improvement on selected academic measures and study skills compared to children of parents randomized to standard care. The study showed high adherence and perceived benefit among parents randomized to the intervention program (Patel et al. 2014b).

Pharmacologic Interventions

Deficits in attention are characterized as a modifiable domain in cognitive dysfunction according to current evidence (Reddick and Conklin 2010). Some aspects of cognitive dysfunction in survivors of pediatric cancer resemble that of attention deficit hyperactivity disorder, inattentive type (ADHD, inattentive type); however, many survivors do not fit the profile for inattention and/or hyperactivity. The most studied medication for treatment of ADHD, inattentive type, is a piperidine derivative, methylphenidate, a mixed dopaminergic-noradrenergic agonist, which enhances function of the fronto-striatal attentional network. Methylphenidate demonstrates a strong dose-response relationship on neurocognitive measures of vigilance, sustained attention, and reaction time in ADHD, inattentive type (Hanwella et al. 2011). Methylphenidate and other stimulant medications have been investigated in studies of childhood cancer survivors with cognitive dysfunction. Treatment with methylphenidate was found to result in improved sustained attention, social skills, and internalizing and externalizing behaviors; however, these benefits did not extend to improved academic performance (Conklin et al. 2009). Male gender, older age at treatment, and higher intellectual functioning at baseline predicted better response to methylphenidate in this later study.

An open-label trial for patients who demonstrated initial response to methylphenidate showed sustained responses after 12 months of continuation therapy, compared with those who did not receive methylphenidate. Parent, teacher, and patient reports were consistent in the treatment group, but not in the control group, where parents reported improvement and teachers and

patients did not (Conklin et al. 2010). Based on these studies, the authors recommend that methylphenidate should be the standard of care for children with cognitive dysfunction who show measurable improvement after short-term use of methylphenidate.

Limitations of methylphenidate studies include cohorts that mix brain tumor and ALL survivors and short half-life of the drug. Importantly, a 5 % rate of dose-limiting side effects was noted with poorer tolerance in survivors of brain tumors compared to those with leukemia (Conklin et al. 2009; Thompson et al. 2001). A COG-randomized trial comparing

Adderall XR™ versus Concerta™ (ACCL0422A) was closed prematurely because of poor participant accrual, which is thought to be in part attributable to the appearance of black box warnings around the use of methylphenidate.

Modafinil, a dopaminergic CNS stimulant, is an alternative treatment to methylphenidate in ADHD, inattentive type. Although not approved by the Food and Drug Administration (FDA) for use in children under the age of 16, it is used off-label to treat narcolepsy, excessive daytime sleepiness, and ADHD, inattentive type (Castellino et al. 2014). Modafinil improved digit span, visual memory, and spatial planning capacity among adult volunteers with cancer, with enhanced benefit among those with lower cognitive capacity at baseline (Kaleita et al. 2006). COG is currently evaluating modafinil in a randomized trial among survivors of pediatric CNS tumors (NCT01381718).

Donepezil is an acetylcholinesterase inhibitor with beneficial effects on cognitive, behavioral, and functional symptoms in Alzheimer's and vascular dementias (Passmore et al. 2005). In a phase II, 24-week, open-label trial of 34 adults with primary brain tumors, donepezil (10 mg/day) resulted in improved attention, concentration, language function, verbal and figure memory, and mood (Rapp et al. 2004). These results formed the basis of an ongoing phase III trial in survivors of adult brain tumors (NCT00369785) and a feasibility trial in childhood brain tumor survivors (NCT00452868). Pilot data in the latter trial indicate good tolerance of the drug, with efficacy in improving executive function and memory over a 6-month, open-label trial (Castellino et al. 2012).

Gaps in Knowledge/Future Directions

As reviewed previously, neuropsychological evaluation is recommended as the standard of care for certain survivor populations who are at an increased risk of experiencing cognitive late effects of treatment. There are a number of cancer treatment centers that follow this guideline. However, to our knowledge, there is no set protocol that is implemented across institutions whereby different centers follow a uniform timeline for neuropsychological evaluations. This type of coordinated assessment approach could provide the opportunity for a large pool of data for future research endeavors. In addition, although neurocognitive screening measures have shown psychometric promise, larger initiatives to routinely integrate these tools into the clinic setting are just beginning and are lacking for broader diagnosis groups (e.g., leukemia). This is another area that is ripe for future growth, especially in the current dynamic health-care climate that calls for more time and resource-sensitive approaches.

Another area clearly in need of further research and consensus pertains to the area of intervention for neurocognitive dysfunction. As reviewed above, there are now several small studies using a variety of interventions and approaches suggestive of preliminary efficacy. Though this is encouraging, the next wave of research also will need to address how to translate the research-based programs into clinical care settings. As this process is initiated, it will also be important to concurrently evaluate the circumstances (disease, level of dysfunction, and patient/family characteristics) under which various intervention approaches or techniques are effective. We need further knowledge on the duration of any benefits and whether booster sessions are needed for benefits to endure over the long term. What is the dose of intervention

required to obtain a minimally positive response in specific outcomes such as academic function? Is a single treatment approach (e.g., child-directed intervention) as effective as a combined treatment approach? It is also important to establish the optimal timing for various treatment approaches: during cancer therapy, soon after completion of therapy, or well into survivorship after deficits have emerged.

Clinical Pearls

- Survivors of acute lymphoblastic leukemia and brain tumors are especially susceptible to adverse cancer-related neurocognitive sequelae; however, children with other cancers may also experience similar difficulties and should be referred for neuropsychological evaluation if clinically indicated.
- Ongoing monitoring for children at risk to develop neuropsychological late effects following completion of cancer therapies is important to identify dysfunction and to facilitate intervention.
- Families need help in understanding their child's neurocognitive issues and establishing special education services at school.
- The degree of neurocognitive and behavioral impairments varies in magnitude based on disease, treatment, and individual factors; therefore, comprehensive neuropsychological evaluation needs to also consider information about the survivor's psychosocial history and functional status across multiple domains to develop a plan that includes a range of therapeutic and educational interventions.
- Yearly comprehensive neuropsychological evaluations may not be feasible or even necessary; consequently, a monitoring strategy that includes a detailed interview about the child's educational and developmental progress and/or abbreviated neurocognitive screenings may be useful in guiding referral for more comprehensive repeated evaluations.
- There is a growing body of intervention research showing preliminary efficacy in improving either cognitive or academic functioning to a modest degree, suggesting that referral to evidence-based, formal cognitive and educational intervention programs may be helpful.

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