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ADHD and Secondary ADHD Criteria Fail to Identify Many At-Risk Survivors of Pediatric ALL and Brain Tumor

Lisa S. Kahalley, PhD¹, Heather M. Conklin, PhD², Vida L. Tyc, PhD², Stephanie J. Wilson, BA², Pamela S. Hinds, PhD RN, FAAN^{3,4}, Shengjie Wu, MS⁵, Xiaoping Xiong, PhD⁵, and Melissa M. Hudson, MD⁶

¹Department of Pediatrics, Section of Psychology, Baylor College of Medicine, Houston TX

²Department of Psychology, St. Jude Children's Research Hospital, Memphis, TN

³Department of Nursing Research and Quality Outcomes, Children's National Medical Center, Washington, DC

⁴Department of Pediatrics, George Washington University, Washington, DC

⁵Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

⁶Department of Oncology, Division of Cancer Survivorship, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Background—Post-treatment attention problems experienced by pediatric cancer survivors have been described as similar to symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) experienced in physically healthy children. Accordingly, the objectives of this study were to: (a) estimate the rate of occurrence of ADHD and secondary ADHD (SADHD) in a sample of pediatric cancer survivors, (b) compare the rate of ADHD/SADHD among survivors to the prevalence of ADHD in the general population, and (c) examine clinical correlates of ADHD/SADHD in this sample.

Procedure—Survivors of pediatric ALL or brain tumor ($n=100$) participated in an assessment of attention including a computerized performance measure [Conners' Continuous Performance Test-II (CPT-II)], parent and self-report measures (Conners 3), and a structured diagnostic interview for ADHD and other psychological disorders [Diagnostic Interview for Children and Adolescents-IV (DICA-IV)].

Results—Binomial tests revealed that the rate of ADHD/SADHD in our sample (9%) was significantly greater than the lower limits of ADHD prevalence among children in the US (3%; $p<0.001$), while no difference was identified compared to the upper limits of ADHD prevalence (7%; $p>0.05$). Many additional survivors (>25% of the sample) obtained clinical elevations on Conners 3 scales but did not meet ADHD/SADHD criteria.

Conclusions—Attentional deficits experienced by pediatric cancer survivors do not appear to resemble the clinical presentation of ADHD or SADHD. Many survivors with cognitive and behavioral difficulties related to attention were not identified using this diagnostic approach. Findings offer needed clarification to guide researchers and clinicians in conceptualizing, assessing, and intervening on attentional late effects.

Corresponding Author: Lisa S. Kahalley, Ph.D., Texas Children's Hospital, 1102 Bates, Suite 730, Houston, TX 77030-2399, US; Telephone: 832-822-4759; Fax: 832-825-4164; lskahall@texaschildrens.org.

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Keywords

cancer; oncology; attention; hyperactivity; ADHD; cognitive assessment; children

Survivors of pediatric brain tumor and acute lymphoblastic leukemia (ALL) are at risk for lasting cognitive impairment attributable to disease and treatments that impact the central nervous system (e.g., cranial radiation therapy, intrathecal chemotherapy) [1-3]. As such, there is growing interest in identifying specific cognitive domains that may be especially vulnerable to disease and treatment in order to focus clinical assessment and guide intervention efforts. In particular, it has been reported that many survivors experience post-treatment deficiencies in attention, concentration, and executive functioning [2,4-11]. Attentional impairment has been identified as a crucial link between treatment-related brain injury and subsequent declines in survivors' intellectual functioning and academic achievement [12]. This underscores the importance of identifying and remediating attentional late effects to improve the long-term functioning of survivors.

The treatment-related attention problems experienced by survivors have been described as similar to the symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), predominately inattentive type, experienced in physically healthy children [13]. Recent findings provide preliminary support for this comparison. Krull and colleagues [14] reported 23% of pediatric leukemia survivors in their sample exhibited clinical elevations on a parent rating scale that assessed the frequency of attention problem symptoms consistent with ADHD. Patel et al. [15] identified 41% of children with a history of brain tumor as having attention dysfunction based on their performance on neuropsychological measures. Further, survivors of pediatric cancer have demonstrated improvement on measures of attentional functioning with pharmacological interventions used traditionally for the treatment of ADHD [i.e., methylphenidate in: 16,17,18], although fewer than half of survivors showed a positive medication response in a recent stimulant trial [19].

ADHD is considered a developmental disorder, as reflected in the diagnostic guidelines that require symptom onset prior to the age of seven years [20]. Still, cognitive and behavioral symptoms consistent with ADHD have been found to result from later acquired central nervous system insult. The term "secondary ADHD" (SADHD), an ADHD presentation acquired from a non-developmental etiology, was first used to describe attention deficits following pediatric traumatic brain injury (TBI) [21]. Estimates of SADHD occurrence after TBI range from 15-23% among children without premorbid ADHD [21-23]. While it is unknown whether developmental ADHD and post-injury SADHD are mediated by similar neurobiological mechanisms, this conceptualization may hold clinical utility given the similarity in behavioral symptoms and potential overlap in appropriate treatments for ADHD and SADHD. SADHD has been examined for nearly a decade within the TBI literature, yet this description, to our knowledge, has never been applied to the presentation of survivors with attentional late effects.

Even though attention problems following treatment for pediatric cancer are frequently studied, the prevalence of ADHD and SADHD among survivors has not been documented. Most studies of attentional late effects have relied upon laboratory measures of sustained visual attention (e.g., continuous performance tests) and/or behavior rating scales to capture survivors' attention functioning. Such instrumentation does not yield definitive information about the presence or absence of ADHD. Clinical practice guidelines state that ADHD assessment should include evidence obtained from multiple sources (e.g., the child, parents, and teachers) about the severity and frequency of symptoms and the level of related functional impairment [24]. The "gold standard" for ADHD assessment includes a

structured clinical interview with caregivers who provide specific information about a child's behavioral functioning and impairment. This interview is used by the clinician to determine whether a child's symptoms meet the diagnostic criteria established in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [20]. In the case of SADHD, the child would meet all diagnostic criteria for ADHD except the age of symptom onset if the central nervous system insult occurred after age seven. Cognitive measures and behavior ratings are important components of a comprehensive clinical evaluation; however, the presence or absence of ADHD cannot be definitively determined by such instrumentation alone.

Drawing from the approach used in TBI research to identify SADHD post-injury, this study aims to clarify the nature of attentional late effects experienced by survivors. Providing nomenclature clarification (i.e., determining whether SADHD appropriately characterizes the late effects experienced by survivors) could offer important guidance to clinicians. Most directly, it could promote clearer communication by strengthening or reducing the conceptual association made between late effects and ADHD. Most families and teachers have some familiarity with the symptoms often exhibited by children with traditional ADHD. If attentional late effects are similar, discussions with families and schools could be improved by referencing this familiar disorder when describing expected late effects symptoms, limitations, and possible interventions. However, if the clinical presentations are dissimilar, distinctions should be made explicitly to prevent survivors from being conceptualized within a clinical framework that does not adequately capture the quality, severity, or functional impact of their deficits. Better understanding of the similarities and differences between these clinical presentations could also guide clinicians in choosing measures that will be most informative in identifying problematic attentional outcomes post-treatment. Since ADHD neurobiology and pharmacology have been extensively researched, determining whether attentional late effects fit an SADHD presentation could lead researchers toward better understanding of the etiology of post-treatment changes and could promote the development of targeted interventions.

The main objectives of this study were to: (a) estimate the occurrence rate of ADHD and SADHD in a sample of adolescent survivors of pediatric ALL or brain tumor, (b) compare the rate of ADHD/SADHD among survivors to the prevalence of ADHD in the general population, and (c) examine clinical correlates of ADHD/SADHD in this sample. It is estimated that 3-7% of physically healthy children and adolescents in the US meet criteria for ADHD [20]. We expected that the total number of patients exhibiting an ADHD or SADHD presentation in our sample of survivors would be significantly higher than the rate of ADHD among healthy children and adolescents in the general population given the elevated rate of attention problems reported in the pediatric oncology literature.

Methods

Patients

Patients were eligible for the study if they had an ALL or brain tumor diagnosis, completed primary treatment at least one year prior to study enrollment, had no evidence of active disease, were between the ages of 12-17 (inclusive), were English-speaking, and were accompanied by an English-speaking parent or legal guardian. Survivors were excluded from participation for documentation of significant intellectual impairment (IQ<70) in the medical record. A total of 100 survivors of pediatric cancer (50 brain tumor, 50 ALL) participated in the study. Demographic and clinical characteristics of the sample are reported in Table I.

Survivors were not excluded for premorbid ADHD diagnosis or related medication. Some survivors had active prescriptions for attention-enhancing medications (e.g., methylphenidate) at the time of study enrollment ($n = 9$), with a few choosing to take their medication on the morning of testing ($n = 4$). In our attempt to identify all survivors currently meeting ADHD/SADHD criteria, it was necessary to include these survivors regardless of medication status. Exclusion likely would have removed the survivors most affected by attentional difficulties from our sample. Differences between those with and without medication were explored.

We enrolled survivors of ALL and brain tumors, despite differences in disease etiology and treatment, given the relevance of attentional late effects to both groups. The composition of this sample was designed to provide generalizability to those survivor groups at greatest risk post-treatment for attention difficulties. Similarly, we chose an inclusion age range of 12-17 years to maximize the detectability of inattentive symptoms and impairment since attentional late effects have been likened to the inattentive symptoms of ADHD [13]. During adolescence, impairment from inattention often becomes more apparent as age-typical increases in academic and household demands cannot be met.

Procedure

Approval from the Institutional Review Board was obtained at the pediatric cancer hospital where this study was conducted and all patients were recruited. Eligible patients were identified by medical record review and were contacted about the study in advance of routine medical visits. Following informed consent and assent procedures, participating survivors completed performance measures and behavior rating scales. One parent or guardian of each patient completed behavior rating scales and participated in a structured diagnostic interview. Parents and guardians provided consent and contact information for the child's primary teacher who completed a rating scale assessing the child's classroom behavior.

Importantly, this study was designed to estimate the frequency of the ADHD and SADHD presentation exhibited within a broad sampling of pediatric cancer survivors. Distinguishing between ADHD and SADHD was beyond the scope of this investigation and would have been challenging (or impossible) for those patients diagnosed with cancer prior to age seven, for whom an ADHD presentation could be attributable to development or treatment-related cause. Instead, we examined the combined proportion of survivors meeting criteria for either ADHD (according to the diagnostic criteria outlined in the DSM-IV) or SADHD (meeting all DSM-IV diagnostic criteria except for the age of onset before 7 years).

Measures

Diagnostic Interview for Children and Adolescents-IV (DICA-IV), Parent Version—The DICA-IV is a computerized, comprehensive structured interview used to assess mental health disorders in children and adolescents according to the diagnostic criteria of the DSM-IV. A licensed clinical psychologist administered DICA-IV modules to parents assessing the patient's history and current presentation of ADHD, behavioral disorders (i.e., Oppositional Defiant Disorder, Conduct Disorder), anxiety disorders (i.e., Generalized Anxiety Disorder, Social Anxiety Disorder, Specific Phobia, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Panic Disorder), and mood disorders (i.e., Major Depressive Episode, Mania, Dysthymia). The DICA is one of the most widely used structured interviews for pediatric mental health assessment research [25]. It is commonly employed in ADHD prevalence and treatment studies with healthy child and adolescent samples [e.g., 26-29] as well as studies of SADHD following TBI [e.g., 21,30,31]. The DICA demonstrated solid test-retest reliability (*median kappa* = 0.87) and

moderate to high agreement across informants (*median kappa* = 0.63) in a clinical sample [32]. Further, the instrument has shown generally strong inter-rater reliability (0.70-0.80) across studies [33]. This clinical interview was used to identify survivors exhibiting an ADHD presentation (i.e., meeting all criteria for ADHD diagnosis) or SADHD presentation (i.e., meeting all criteria for ADHD except the age of onset) at the time of the evaluation.

Conners' Continuous Performance Test-II (CPT-II)—Survivors completed the CPT-II, a performance-based measure of attention, which is used frequently in studies of the cognitive outcomes of pediatric cancer [e.g., 12,16,18,34-36]. This is a norm-based, computerized test assessing specific components of attention during a visual-motor task. This 14-minute task requires the participant to watch a random series of letters presented one at a time on the computer screen. Participants press the space bar each time a letter appears on screen, except for the letter “X.” Specific outcomes examined in this study include: errors of omission (where high scores (many errors) could indicate inattentiveness to task), errors of commission (where high scores (many errors) could indicate impulsive responding), hit reaction time (where high scores indicate slow responding and low scores indicate fast responding), and detectability (where high scores could indicate difficulty with rapid discrimination between targets and nontargets). Internal consistency ranges from good to excellent across these indexes ($r = 0.83-0.95$) [37]. The CPT-II has demonstrated the ability to distinguish between clinical and non-clinical groups [37], although limitations have been noted elsewhere regarding the specificity [38,39] and sensitivity [38,40] of the measure. Norm-derived T-scores have a mean of 50 and standard deviation of 10.

Conners 3rd Edition™ (Conners 3)—Three versions of the Conners 3 were administered in this study (self-, parent-, and teacher-report). This measure assesses cognitive, emotional, and behavioral symptoms associated with ADHD and related disorders. Standardization based on a large, representative national sample demonstrated strong psychometric properties [41], with internal consistency reliability across scales ranging from 0.81-0.90 (self-report), 0.83-0.94 (parent-report), and 0.78-0.97 (teacher-report). The ADHD Index reliably distinguished between youth with and without an ADHD diagnosis, and the factor structure exhibited stability in cross validation. Norm-derived T-scores have a mean of 50 and standard deviation of 10.

Statistical Analyses

This study was intended to provide descriptive information about survivors meeting diagnostic criteria for ADHD or SADHD, not to provide conclusive evidence of SADHD resulting from disease and treatment. The binomial test was used to compare the proportion of survivors meeting ADHD/SADHD criteria to the prevalence of ADHD among healthy children and adolescents in the US. If the proportion of survivors meeting ADHD/SADHD criteria exceeds the upper limit expected for ADHD in the general population, results would provide preliminary support that an SADHD presentation may develop as a consequence of cancer and treatment. Fisher's exact test and Wilcoxon rank sum test were used to identify relationships between the DICA-IV classification (ADHD/SADHD versus No ADHD/SADHD) and demographic, clinical, and behavioral variables. The significance level ($p < 0.05$) was not adjusted for multiple comparisons since this study was intended to provide preliminary descriptive results.

Results

Occurrence of ADHD/SADHD

Only nine out of 100 survivors met criteria for ADHD ($n = 4$) or SADHD ($n = 5$) based on the DICA-IV assessment. Since we are unable to definitively distinguish between a

developmental or acquired etiology of the attention problems in the current study, we grouped these survivors together as ADHD/SADHD. The presence of six or more persistent symptoms of inattention or hyperactivity/impulsivity is required for an ADHD diagnosis. All nine survivors exhibited six or more symptoms of inattention, but only one of those exhibited six or more hyperactive-impulsive symptoms.

Binomial tests were used to compare the rate of ADHD/SADHD in our sample (9%, with 95% CI: 4.2%, 16.4%) to the lower and upper limits of the ADHD prevalence among children and adolescents in the US (3% and 7%, respectively) [20]. Significantly more survivors met criteria for ADHD/SADHD compared to the more conservative estimate of 3% for US children with ADHD ($z = 3.52, p < 0.001$); however, no difference was identified compared to the 7% prevalence estimate ($z = 0.78, p = 0.43$).

Correlates of ADHD/SADHD

Demographic and clinical characteristics—Fisher's exact tests and Wilcoxon rank sum tests were used to identify demographic variables and clinical characteristics associated with DICA-IV classification (ADHD/SADHD vs. No ADHD/SADHD). Significance values are reported in Table I. More males met criteria for ADHD/SADHD than females, although the difference was not statistically significant ($p = 0.16$, Fisher's exact test). No other demographic or medical variables were found to be significantly associated with DICA-IV classification, including diagnosis, age at diagnosis, and treatment history.

Performance measures and behavior ratings—The Wilcoxon rank sum test was used to identify performance measures and behavior ratings associated with DICA-IV classification. Means and significance values are reported in Table II. Survivors with ADHD/SADHD exhibited slower reaction time on the CPT-II compared to those without ADHD/SADHD ($Mdn_{ADHD/SADHD} = 48.7, Mdn_{None} = 42.9, p < 0.05$), but no other CPT-II indexes were significantly associated with DICA-IV classification. In contrast, survivors with ADHD/SADHD received significantly higher (more problematic) scores on many of the Conners 3 scales completed by parents and teachers. On the parent-report Conners 3, survivors with ADHD/SADHD exhibited more inattention ($Mdn_{ADHD/SADHD} = 71.0, Mdn_{None} = 54.0, p < 0.001$), hyperactivity/impulsivity ($Mdn_{ADHD/SADHD} = 68.0, Mdn_{None} = 48.0, p < 0.01$), and executive dysfunction ($Mdn_{ADHD/SADHD} = 73.0, Mdn_{None} = 51.0, p < 0.001$), and received higher ADHD Index ($Mdn_{ADHD/SADHD} = 77.0, Mdn_{None} = 20.0, p < 0.001$) and Global Index scores ($Mdn_{ADHD/SADHD} = 67.0, Mdn_{None} = 52.0, p < 0.01$) compared to those without ADHD/SADHD. In addition, these survivors exhibited more symptoms of Conduct Disorder ($Mdn_{ADHD/SADHD} = 51.0, Mdn_{None} = 45.0, p < 0.05$) and Oppositional Defiant Disorder ($Mdn_{ADHD/SADHD} = 60.0, Mdn_{None} = 49.0, p < 0.05$) compared to survivors without ADHD/SADHD. Similarly, based on teacher ratings on the Conners 3, survivors with ADHD/SADHD were more inattentive ($Mdn_{ADHD/SADHD} = 63.0, Mdn_{None} = 45.0, p < 0.01$) and hyperactive/impulsive ($Mdn_{ADHD/SADHD} = 60.0, Mdn_{None} = 45.0, p < 0.01$) than survivors without ADHD/SADHD. They also experienced more executive dysfunction ($Mdn_{ADHD/SADHD} = 54.0, Mdn_{None} = 46.0, p < 0.05$) and had higher ADHD Index ($Mdn_{ADHD/SADHD} = 64.0, Mdn_{None} = 19.0, p < 0.01$) and Global Index scores ($Mdn_{ADHD/SADHD} = 70.0, Mdn_{None} = 44.0, p < 0.01$). Additionally, these survivors expressed more behaviors of defiance and aggression ($Mdn_{ADHD/SADHD} = 64.5, Mdn_{None} = 45.0, p < 0.01$) and exhibited more symptoms of Conduct Disorder ($Mdn_{ADHD/SADHD} = 53.0, Mdn_{None} = 46.0, p < 0.05$) and Oppositional Defiant Disorder ($Mdn_{ADHD/SADHD} = 75.0, Mdn_{None} = 45.0, p < 0.001$) than survivors without ADHD/SADHD. No associations were found between ADHD/SADHD classification and learning problems (parent- or teacher-report), peer relations (parent- or teacher-report), or any domains on the Conners 3 self-report form.

Characteristics of Survivors with and without ADHD/SADHD

Characteristics of the nine survivors classified as ADHD/SADHD are reported in Table III. Survivors with ADHD/SADHD were significantly more likely to meet criteria for at least one other psychological disorder (66.7%) on the DICA-IV than were survivors without ADHD/SADHD (18.7%) in this sample ($p < 0.01$, Fisher's exact test).

Many survivors who did not meet ADHD/SADHD criteria still appeared to experience problematic functioning in many domains on parent and teacher rating scales. Table II reports the percentage of participants that received clinically concerning elevations (defined as T-scores ≥ 65) across Conners 3 scales by ADHD/SADHD classification. Across raters, learning problems were particularly frequent, identified in 21-26% of survivors without ADHD/SADHD. Inattention occurred in 11-19% of survivors without ADHD/SADHD. Most survivors who met ADHD/SADHD criteria obtained clinical elevations on many scales. Alternatively, the majority of survivors who obtained clinical elevations did not meet ADHD/SADHD criteria.

Three of the nine survivors who met criteria for ADHD/SADHD had active prescriptions for attention-enhancing medications. The other six survivors in the sample with prescriptions did not meet ADHD/SADHD criteria. As a group, survivors prescribed medication had significantly higher scores on most parent-report scales (Inattention, Hyperactivity/Impulsivity, Executive Functioning, Peer Relations, ADHD Index, and Global Index) on Wilcoxon rank sum tests (all $p < 0.05$) compared to those without medication. Survivors with prescriptions also received higher teacher ratings on the Inattention and Conduct Disorder scales as well as the ADHD Index compared to un-medicated survivors (all $p < 0.05$). No differences in CPT-II performance were detected between survivors prescribed medication ($n = 9$) or those who took medication on the day of testing ($n = 4$) when compared to the rest of the sample, although the low frequency of these events may have prevented the detection of small effects.

Discussion

Contrary to our hypothesis, the occurrence of ADHD and SADHD among survivors was relatively infrequent (9%) in this sample. This rate was consistent with the upper limits of the prevalence rate reported for ADHD among healthy children and adolescents in the US (3-7%) [20]. More importantly, the diagnostic criteria for ADHD/SADHD failed to identify many other survivors suffering from post-treatment behavioral dysfunction. We conclude that conceptualizing attentional late effects as similar to the clinical presentation of ADHD may not be accurate or useful. We consider this finding to be especially valuable for the purpose of nomenclature clarification. Based on our results, SADHD does not resemble the typical presentation of post-treatment attentional dysfunction experienced by survivors in the way it does for many children following TBI [21-23].

Many survivors experiencing cognitive and behavioral difficulties based on parent and teacher rating scales were not classified as ADHD/SADHD. This classification finding could imply that a structured clinical interview assessing standard diagnostic criteria for ADHD/SADHD lacks sensitivity to capture attentional late effects. Alternatively, the diagnostic criteria for ADHD and SADHD may be unrepresentative of late effects and too restrictive to adequately capture all affected survivors. The high number of survivors with elevated scores on behavior rating scales (across reporters) suggests that attention problems and related impairment are more common than represented by the 9% ADHD/SADHD rate. Importantly, the similarities between ADHD/SADHD and post-treatment attentional functioning seem limited to symptoms of inattention only, with only one survivor classified as ADHD/SADHD meeting the threshold for hyperactive-impulsive symptoms. The

frequency of learning problems represented in this sample suggests that problems with attention identified on these rating scales may represent global cognitive dysfunction rather than actual attentional deficits. Overall, it appears that ADHD does not adequately represent the post-treatment experience for most affected survivors.

The ADHD/SADHD rate was higher (but non-significant) in males in our sample, which is consistent with gender trends in the general population [42]. Survivors classified as ADHD or SADHD in this sample also met criteria for other behavioral, depressive, and anxiety disorders, paralleling the high frequency of comorbidity between ADHD and other emotional and behavioral disorders represented in the general population [42]. It appears that these survivors are at risk for a multiplicity of psychosocial difficulties, and comprehensive assessment is warranted for those who exhibit an ADHD presentation.

Many studies of attention in pediatric oncology exclude patients with a premorbid ADHD diagnosis [e.g., 6,7,16]. While this provides a purer examination of cognitive late effects, it limits our understanding of post-treatment functioning for patients who could be particularly vulnerable to the neurological complications of treatment. For our purposes, inclusion of these patients was essential to estimate the number of survivors currently meeting ADHD or SADHD criteria following treatment for ALL and brain tumor. Clearly, our methodology for assessing ADHD/SADHD at a single time point after treatment prevents definitive etiological conclusions (developmental vs. treatment-related) from being drawn. In fact, differentiating between ADHD and SADHD in survivors may be futile. The onset of cancer can occur prior to age seven, as seen in 55% of our sample, which is the maximum age of symptom onset according to standard ADHD diagnostic criteria. Therefore, determining whether an ADHD presentation would have developed with or without cancer and treatment is impossible for a sizeable number of patients. Even so, the need to distinguish between ADHD and SADHD would be particularly crucial if it appeared that SADHD was prevalent in this population and if the conceptualization seemed to be an appropriate way to identify survivors at greatest risk of post-treatment attentional deficits. However, our results suggest this is not the case.

The rate of ADHD/SADHD in our sample contrasts with the findings of a recent study examining genetic polymorphisms predictive of survivors' attentional functioning. Krull et al. [14] reported nearly one quarter of ALL survivors in their sample could be classified as exhibiting ADHD based on parent ratings on the Child Symptom Inventory. The difference in rates between that study and our current findings is likely due to differing measurement approaches. Our classifications of ADHD or SADHD involved a comprehensive, structured, clinical interview that assessed ADHD symptoms according to DSM-IV diagnostic criteria. This methodology, recommended in current clinical practice guidelines [24], likely yielded a more restrictive approach to classification than the methods employed by Krull et al. Finding few survivors who met ADHD/SADHD criteria in our study does not mean that survivors are not exhibiting attentional late effects. Instead, it indicates that this diagnostic approach and the ADHD/SADHD conceptualization are not the most useful for assessing and characterizing late effects in this population.

There is a growing literature suggestive of differences in the symptom presentation of children with ADHD and those previously treated for cancer. In a methylphenidate trial with survivors exhibiting attentional deficits, Conklin et al. [19] determined that fewer survivors experienced clinically significant benefits from medication than expected from response rates in most medication trials conducted with healthy ADHD samples. We identified only one published study actually comparing attentional functioning between survivors of pediatric cancer and children with ADHD [43]. Researchers compared performance on a computerized continuous performance test across participants diagnosed with ADHD, TBI,

insulin-dependent diabetes mellitus, and pediatric ALL. No differences in performance were detected between healthy controls and ALL survivors, while the ADHD group exhibited significantly weaker performance than controls across all attention indices measured.

Future efforts should focus on better discrimination of the deficits experienced by survivors. A well known series of studies has examined stimulant medication to treat attentional late effects among survivors of ALL and brain tumor [16-19]. When considering the results of the methylphenidate trials, it is important to recognize that most individuals, not just those with attentional impairment, demonstrate improved performance after taking stimulant medications [44-46], and such medications can enhance performance by acting on processes other than attention, such as response speed [47]. While the use of methylphenidate to ameliorate symptoms in survivors may suggest a similarity in clinical presentation or etiology between ADHD and attentional late effects, no studies to date have examined these similarities specifically.

Questions remain about the quality of attentional late effects experienced by survivors. Many measures commonly used to assess post-treatment attentional late effects also assess related functions (e.g., processing speed, working memory, visual-motor control). For example, many late effects studies have used computerized continuous performance tests to assess attention problems [e.g., 12,18,34-36,48], although these tasks also involve notable speed and visual-motor demands. As such, it remains unclear the extent to which deficient performance on these tasks by survivors is best described as inattention or as another type or combination of deficits (e.g., slow processing). Similarly, Reeves and colleagues [49] reported that ALL survivors exhibit behavioral symptoms consistent with a “sluggish cognitive tempo” (SCT). SCT refers to a symptom cluster associated with a subset of individuals with ADHD who are lethargic, disorganized, and dreamy [50]. The study compared parent ratings on five items of the Child Behavior Checklist (CBCL) [51] descriptive of the SCT presentation in healthy samples [52,53]. Results determined that survivors exhibited significantly more SCT symptoms than sibling controls, and elevated SCT scores were associated with lower intellectual and achievement scores. It remains unclear if the survivors' elevated SCT scores were actually indicative of an independent SCT construct or were merely an artifact of elevations across all items from the Attention Problems scale, which could represent general attentional difficulty alone or in addition to SCT.

Our findings must be considered in light of certain methodological limitations. First, our sample included survivors of a restricted age range (12-17 years) assessed at a single time point. It is possible that the rate of ADHD/SADHD in our sample could underestimate the prevalence among survivors if symptoms are likely to remit during adolescence. While early conceptions of ADHD assumed recovery for most individuals after childhood, current views, supported by strong longitudinal research, characterize the disorder as chronic, persisting through adolescence for most [42]. Further, the course of cognitive late effects typically involves onset within one year post-treatment with a stable or worsening course over time [3]. Still, the cross-sectional design of our study limits conclusions about the onset of symptoms or stability of presentation over time in this group. Second, small sample size may have limited our ability to detect differences in ADHD/SADHD classification on other relevant clinical variables, including diagnosis, age at diagnosis, and treatment history, given the relatively low base rate of ADHD and SADHD identified in this sample. Third, survivors were not excluded from our study for holding active prescriptions for attention-enhancing medications since those survivors were likely to be the very ones most affected by attentional difficulties. If we chose to exclude survivors with prescriptions ($n = 9$), we would have significantly underrepresented the number of survivors meeting ADHD/SADHD criteria (e.g., 33% of survivors with ADHD/SADHD also held active prescriptions).

Certainly, taking medication prior to testing could impact performance on the CPT-II. Further, survivors who took medication regularly prior to the evaluation could have earned more favorable ratings on behavior scales and their parents could have endorsed fewer symptoms or less impairment in the clinical interview, based on the child's medication-enhanced behavior. However, this is less likely given that group comparisons of behavior ratings showed that survivors with active prescriptions were more impaired than their unmedicated counterparts. While future studies might specify a medication washout period prior to study assessment, exclusion of survivors for medication use or for prior ADHD diagnosis could result in a significant misrepresentation of the occurrence and severity of related late effects.

Conclusion

Further work is needed to advance our understanding of the quality, severity, and functional impact of attentional late effects experienced by some pediatric cancer survivors. Our findings offer necessary information for nomenclature clarification. It appears that ADHD and SADHD do not appropriately characterize the late effects experienced in this sample. This clarification should redirect our discussions about attentional late effects. Researchers and clinicians alike may benefit to think differently about the difficulties survivors experience post-treatment, rather than likening them to the symptoms of ADHD. For instance, assessment should include specific measures of attention but should not neglect other related processes that could better explain performance discrepancies (e.g., slow information processing, working memory difficulties). In terms of intervention, the approach to remediation in the classroom differs according to the nuances of a child's specific deficits. For example, a child who is inattentive may require a structured behavior plan with frequent redirection to task and positive reinforcement of time on task within the classroom. In contrast, a child who processes information slowly may be able to attend adequately to a lesson but requires more time to process new information and to respond to questions and test items and may require shortening of assignments to reduce fatigue and frustration. This distinction has notable practical implications for the clinician advocating for school services and may also bear significant consequence for the long-term outcome of the survivor. Further, most post-treatment attentional difficulties appear to resemble inattention. This presentation may differ from what many parents and teachers expect based on their traditional understanding of ADHD (e.g., hyperactivity and impulsivity), thereby limiting the usefulness of the SADHD conceptualization for these caregivers. This study represents a step toward developing a more sophisticated understanding of the cognitive and behavioral deficits experienced post-treatment necessary to guide assessment and promote the development and prescription of appropriate interventions for this population.

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ALL	acute lymphoblastic leukemia
SADHD	secondary Attention-Deficit/Hyperactivity Disorder

Table 1
Demographic and Clinical Characteristics of Survivors and Univariate Comparisons by ADHD/SADHD Classification

Characteristic	All Participants		ADHD/SADHD		No ADHD/SADHD		<i>p</i>
	<i>N</i>	%	<i>n</i>	Row %	<i>n</i>	Row %	
Total	100	100.0	9	9.0	91	91.0	
Diagnosis							
Brain tumor	50	50.0	5	10.0	45	90.0	0.999
ALL	50	50.0	4	8.0	46	92.0	
Sex							
Female	50	50.0	2	4.0	48	96.0	0.160
Male	50	50.0	7	14.0	43	86.0	
Race/ethnicity							
White, non-Hispanic	85	85.0	7	8.2	78	91.8	0.621
Non-White	15	15.0	2	13.3	13	86.7	
Cranial Radiation							
No	53	53.0	3	5.8	50	94.2	0.299
Yes	47	47.0	6	12.5	41	87.5	
Chemotherapy							
No	24	24.0	3	12.5	21	87.5	0.445
Yes	76	76.0	6	7.9	70	92.1	
	M ± SD	Range	M ± SD	Range	M ± SD	Range	<i>p</i>
Age at study participation	15.0 ± 1.9	12.1 – 18.0	15.7 ± 1.6	12.6 – 17.8	14.9 ± 1.9	12.1 – 17.9	0.208
Age at diagnosis	6.6 ± 3.8	0.7 – 15.2	7.9 ± 3.7	3.3 – 15.0	6.4 ± 3.7	0.7 – 15.2	0.282
Years since diagnosis	8.4 ± 3.9	1.7 – 16.9	7.8 ± 3.3	2.8 – 13.2	8.5 ± 4.0	1.7 – 16.9	0.584
Years since chemotherapy	6.8 ± 3.5	1.4 – 15.5	5.5 ± 3.0	2.3 – 10.8	6.9 ± 3.5	1.4 – 15.5	0.272
Years since radiation therapy	5.6 ± 3.5	1.2 – 15.8	6.2 ± 3.4	2.5 – 11.9	5.5 ± 3.5	1.2 – 15.8	0.582

Note. *p*-values are reported for comparisons of DICA-IV classification (ADHD/SADHD vs. No ADHD/SADHD) across demographic and clinical variables using Fisher's exact test for dichotomous and Wilcoxon rank sum test for continuous variables.

Table II
Means and Clinical Elevations on Psychological Outcome Measures by ADHD/SADHD Classification

Measure	ADHD/SADHD			No ADHD/SADHD		
	<i>n</i> ^a	Mean ± SD	% Clinical	<i>n</i> ^a	Mean ± SD	% Clinical
CPT-II						
Omissions	9	48.5 ± 6.7	0.0%	87	47.1 ± 6.8	3.4%
Commissions	9	45.9 ± 15.1	22.2%	87	50.3 ± 10.8	9.2%
Hit RT	9	50.1 ± 8.9	11.1%	87	43.1 ± 10.1	2.3%
Detectability	9	46.2 ± 12.4	0.0%	87	50.8 ± 8.8	4.6%
Conners3 (parent-report)						
Inattention	9	75.8 ± 12.8	88.9%	90	55.0 ± 11.8	18.9%
Hyperactivity/Impulsivity	9	67.1 ± 18.5	55.6%	91	51.8 ± 10.2	12.1%
Learning Problems	9	65.8 ± 17.0	33.3%	91	57.0 ± 14.4	26.4%
Executive Functioning	9	71.1 ± 7.9	88.9%	91	53.7 ± 10.9	14.3%
Defiance/Aggression	9	61.8 ± 20.6	33.3%	91	50.0 ± 10.0	9.9%
Peer Relations	9	79.0 ± 34.9	66.7%	91	60.5 ± 21.9	25.3%
CD	9	60.9 ± 19.2	33.3%	91	49.3 ± 8.2	6.6%
ODD	9	67.2 ± 23.7	44.4%	91	51.5 ± 9.4	9.9%
ADHD Index	9	76.7 ± 17.7	66.7%	90	33.2 ± 26.8	13.3%
Global Index	9	73.9 ± 21.8	55.6%	90	53.5 ± 10.5	14.4%
Conners3 (teacher-report)						
Inattention	9	68.4 ± 20.0	44.4%	76	49.1 ± 10.6	10.5%
Hyperactivity/Impulsivity	9	65.8 ± 19.9	44.4%	76	47.0 ± 6.6	2.6%
Learning Problems	9	64.1 ± 22.0	33.3%	75	55.2 ± 13.9	21.3%
Executive Functioning	9	59.7 ± 16.6	33.3%	75	48.3 ± 8.8	4.0%
Defiance/Aggression	8	73.1 ± 38.8	50.0%	76	46.6 ± 3.7	0.0%
Peer Relations	9	62.4 ± 22.1	22.2%	75	52.7 ± 13.2	16.0%
CD	8	64.5 ± 29.9	25.0%	76	46.2 ± 3.8	0.0%

Measure	ADHD/SADHD			No ADHD/SADHD			p
	n ^a	Mean ± SD	% Clinical	n ^a	Mean ± SD	% Clinical	
ODD	9	79.0 ± 37.9	55.6%	76	48.1 ± 6.0	2.6%	0.000***
ADHD Index	9	55.8 ± 32.2	44.4%	76	26.0 ± 15.5	3.9%	0.001**
Global Index	9	71.8 ± 26.5	55.6%	76	48.0 ± 8.6	6.6%	0.004**
Conners3 (self-report)							
Inattention	9	53.9 ± 11.4	33.3%	90	53.5 ± 11.5	17.8%	0.826
Hyperactivity/Impulsivity	9	51.8 ± 7.8	11.1%	91	52.1 ± 9.4	11.0%	0.947
Learning Problems	9	51.2 ± 8.2	0.0%	90	55.6 ± 13.0	21.1%	0.472
Defiance/Aggression	9	49.8 ± 14.4	11.1%	91	48.6 ± 10.5	11.0%	0.880
Family Relations	9	48.6 ± 6.9	0.0%	91	47.7 ± 7.7	3.3%	0.484
CD	9	49.4 ± 11.0	11.1%	91	48.0 ± 11.4	9.9%	0.400
ODD	9	52.3 ± 7.2	11.1%	91	50.0 ± 9.1	6.6%	0.323
ADHD Index	9	49.6 ± 11.9	11.1%	90	43.9 ± 19.1	17.8%	0.144

Note. Reported scores are T-scores (mean = 50, SD = 10). Higher scores indicate more problematic functioning. Clinical elevations were defined as T-scores ≥ 65. *p*-values are reported for Wilcoxon rank sum tests comparing means by DICA-IV classification (ADHD/SADHD versus No ADHD/SADHD).

^a *n*s vary across Conners 3 content scales when scores were not calculated due to skipped items (*n* = 1 across parent-, self-, and teacher-report forms), teacher-report forms not returned by teachers (*n* = 7), and teacher-report forms not included for parent-instructed homeschooled children (*n* = 8). CPT-II scores were not available for patients who could not participate due to visual impairment (*n* = 2) and who fell asleep during task administration (*n* = 2).

* *p* < 0.05,

** *p* < 0.01,

*** *p* < 0.001.

Table III
Characteristics of Survivors Meeting ADHD/SADHD Classification

Patient #	Age	Sex	Diagnosis	Age at Diagnosis	Treatment	Stimulant Medication	Other DICA-IV Disorder		
							Behavioral	Mood	Anxiety
1	12.6	F	ALL	3.3	Chemo	Yes*	x		
2	14.5	F	BT	5.6	RT + Surgery	Yes*			x
3	14.5	M	BT	9.0	RT + Chemo + Surgery	Yes**			
4	15.5	M	BT	10.4	RT + Chemo + Surgery	No	x	x	x
5	15.7	M	BT	7.1	Surgery	No	x		x
6	16.5	M	ALL	10.9	RT + Chemo	No		x	x
7	16.9	M	ALL	5.8	Chemo	No			
8	17.3	M	ALL	4.1	RT + Chemo	No	x		x
9	17.8	M	BT	15.0	RT + Surgery	No			

Note. Age reported in years.

* Prescribed stimulant medication for daily use; medication taken as prescribed on the day of testing.

** Prescribed stimulant medication for daily use; medication not taken on the day of testing.