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Symptoms of Attention-Deficit/Hyperactivity Disorder in Long-Term Survivors of Childhood Leukemia

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Abstract

Background—Survivors of childhood acute lymphoblastic leukemia (ALL) sometimes have clinical features that suggest Attention-Deficit/Hyperactivity Disorder (ADHD), though few studies have examined specific symptoms in survivors.

Procedure—Long-term survivors of childhood ALL (n=161) received a neurological examination, while parents completed rating scales to establish formal criteria for ADHD. Symptom profiles were generated and compared across demographic and treatment characteristics, as well as medical tests associated with brain pathology.

Results—Prevalence rates of ADHD were similar in survivors (10.5%) compared to those reported in the general population (7–10%). However, 25.5% of survivors reported symptoms that impair functioning in multiple settings, with attention problems being most common. These symptoms were associated with cranial radiation therapy (CRT) (mean inattentive symptoms [SD] = 3.6 [3.19] for group treated with CRT vs. 1.6 [2.40] for non-CRT group, p=0.0006), and survivors who demonstrated impaired anti-saccades during the neurologic exam (mean inattentive symptoms [SD] = 3.4 [3.29] for those with impaired anti-saccades vs. 1.4 [2.41] for those with normal anti-saccades; p = 0.0004).

Conclusions—The presence of a neurologically-based phenotype of attention problems in survivors of leukemia that is not fully captured by the syndrome of ADHD suggests that treatments specific to childhood ALL should be explored.

Keywords

ALL; long-term survivor; Attention-Deficit/Hyperactivity Disorder

INTRODUCTION

Neurocognitive impairment is estimated to occur in 20–40% of long-term survivors of childhood acute lymphoblastic leukemia (ALL).[1,2] Abnormalities in specific neurocognitive skills, particularly processing speed, attention, and working memory, have been reported.[3–5] In addition, many survivors have been reported to display behavioral symptoms of attention deficits, [4,6,7] which are to be distinguished from impaired neurocognitive measures of attention by virtue of the fact that they are assessed through behavioral ratings rather than direct measures of performance. In a recent survey involving

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2,979 adolescent survivors of cancer, children with ALL were identified as having significantly higher rates of parent-reported attention deficits compared to sibling controls.[8]

Although neurocognitive and behavioral problems are often attributed to the effects of cranial radiation, central nervous system (CNS) treatment with chemotherapy has also been implicated.[9–12] Recent studies have demonstrated poor neuropsychological outcomes in survivors of childhood ALL treated with intravenous or intrathecal methotrexate.[13] Such treatment has been associated with not only reduced function, but also neuroimaging abnormalities in ALL survivors.[14] In a large retrospective multicenter study, magnetic resonance imaging (MRI) scans of brain were abnormal in 52% of pediatric ALL survivors.[15] Rates of MRI abnormality were higher in children who received cranial irradiation, though 39% of children treated with chemotherapy alone also demonstrated neuroanatomical abnormalities. Prospective brain MRI studies reveal rates of leukoencephalopathy as high as 86% shortly after high dose intravenous methotrexate, with a reduction to approximately 30% prevalence by the end of therapy.[14] Notably, the occurrence of acute leukoencephalopathy has been associated with reduced performance on sustained attention tasks.[16]

The problems in performance-based measures of sustained attention and behavioral reports of attention deficits among ALL survivors has led some to question whether a diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) is warranted.[2] Distinguishing “attention problems” from “ADHD” is important with respect to underlying etiology and potential treatment options. ADHD is a syndrome of clearly defined symptoms of pervasive and persistent problems with inattention and/or combined impulsivity and hyperactivity, as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[17] The diagnosis requires 1) a sufficient number of symptoms (six of nine possible inattentive or hyperactive/impulsive symptoms); 2) the presence of symptoms in multiple settings; and 3) functional impairment associated with the symptoms. Reduced concentration may limit performance on single or multiple laboratory-based measures of attention, but, may not be associated with a disruption of daily life functioning. If poor performance on a laboratory-based attention task does not correspond with disruption in daily functioning, treatment of the symptom would not necessarily be recommended. Similarly, behavioral observations of attentive deficits may stem from a variety of etiologies (e.g. depression, fatigue), and would only reach a syndrome level if the behavior disrupts multiple daily life functions in multiple settings. Only pervasive and persistent attention deficits warrant the diagnosis of ADHD and, perhaps, the risks associated with medication management.[18,19]

The purpose of the current study was to estimate the occurrence of ADHD symptoms in a large sample of survivors of childhood ALL. An ADHD specific rating scale was used to evaluate the children according to established diagnostic criteria.[17] Symptom patterns were examined in light of treatment characteristics and neurological signs of brain impairment.

METHODS

All prospective data was collected after approval of the Institutional Review Board (IRB) at St. Jude Children’s Research Hospital. Written informed consent was obtained from the patients who were 18 years of age, and in the case of younger patients, from the parents or guardians, with assent from the child participant, as appropriate.

Participants

Using institutional databases, 161 long-term ALL survivors were recruited from active follow-up clinics. Survivors were between 6–28 years of age (Mean=16.2, SD=5.04) and were at least five years (Mean=10.7, SD=4.20) from diagnosis of cancer. Twenty-eight survivors (17.4%) were at least 21 years of age at the time of participation, though only 4 (2.5%) were identified as living outside of their parent's home at the time of participation. Survivors were excluded from the study if a recurrent or secondary cancer had been identified in the previous year. Proficiency in reading English was required for participation. Survivors with pre-existing non-cancer related neurological disorders which, in the judgment of the attending neurologist, would potentially confound clinical observation were also deemed ineligible for the study. During the period of recruitment, 432 potentially eligible ALL survivors were seen at the institution. Inability to coordinate patient schedule with study personnel availability limited study recruitment, such that 260 eligible survivors were approached for recruitment. Of these, 232 agreed to participate (89.2% consent rate), though 58 of the consented patients could not be scheduled during their annual visit, due to lack of availability on the patient's (n=8) or the physician's (n=50) schedule. In addition, 13 of the 174 patients scheduled did not show up for their appointment and were not able to be re-scheduled prior to their departure. Thus, the 161 patients included in this study reflect 79.7% of the 202 patients who were eligible, approached, and available for participation during their annual follow-up visit. However, as demonstrated in Table I the 161 survivors successfully recruited and evaluated did not substantially differ from those not recruited on key demographic (e.g., sex, age at diagnosis) or treatment (e.g., cranial radiation) characteristics.

Medical records of all potential study participants were abstracted for salient treatment and medical history information. Of the 161 total participants, 151 (93.8%) underwent routine neuroimaging during active ALL therapy as part of a prospective study to investigate rates of therapy-induced leukoencephalopathy. These images were coded as to the presence of leukoencephalopathy based on a review of radiology reports for patients participating in the current study.

Study Measures

After enrollment, all participants completed a questionnaire and a neurological examination. The questionnaire was administered by trained study personnel with the parent serving as the primary respondent. The questionnaire consisted of items designed to establish the presence, to further characterize, and to determine the degree of impairment resulting from specific neurobehavioral symptoms. Symptoms of interest for the current study included the 18 symptoms of ADHD using a format consistent with the Vanderbilt Attention-Deficit Hyperactivity Disorder Parent Rating Scale,[20] and based on formal diagnostic criteria from the DSM-IV.[17] For these primary ADHD symptoms, parents are asked to report the frequency of occurrence of each symptom on a four-point Likert scale (0=Never, 1=Occasionally, 2=Often, 3=Very Often). Additional questions are included for the parent to provide assessment of the impact of these symptoms on the survivors' daily life. ADHD specific rating scales have demonstrated excellent reliability and concurrent validity with formal psychiatric diagnosis.[20] Such scales have been recommended by the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry to establish an initial diagnosis of ADHD.[21,22] Two additional questions were also included to assess previous diagnosis of ADHD and previous use of stimulant medication. This rating scale was completed by parents of the survivors in order to assess a persistent and pervasive pattern of symptoms. Parents were chosen as respondents to ensure consistency of rater across age ranges and due to the fact that the validity of self-reported ADHD symptoms has

been questioned in the literature. [23–25] The primary guardian of the survivor was the respondent, this typically being the mother.

Every participant underwent a comprehensive, standardized neurological examination by a board-certified child neurologist (RBK, EBM). The evaluation assessed cranial nerve function, muscle strength/tone/reflexes, balance, coordination, and sensory systems. In addition, subtle neurological signs according to the Zurich Neuromotor Scale were assessed. [26] For the purpose of this study, we have examined correspondence of ADHD symptoms to two complex neuromotor tasks: sequential hand movements and anti-saccade movements. These tasks were selected because of their association with higher cortical functions typically impaired in ADHD.[27–30]

Statistical Analysis

Descriptive statistics were generated and the frequency of occurrence for each symptom severity was calculated. Consistent with previous reports, [31] abnormal symptoms that were reported to occur either “Often” or “Very Often” were considered to meet the threshold for impairment and coded as a positive symptoms of ADHD. Survivors were then classified into groups based on whether or not they met diagnostic criteria for ADHD. This classification was based on the three subtypes of ADHD (i.e. Inattentive, Hyperactive/Impulsive, or Combined), with the subtype defined as meeting at least six of the nine inattentive symptoms, six of the nine hyperactive/impulsive symptoms, or both categories of inattentive and hyperactive symptoms, respectively.[17] Associations between the number of positive ADHD symptoms and demographic, treatment, and neurological signs of brain impairment were then examined using t-tests.

RESULTS

As seen in Table I, 55% of the sample was female and most were less than 10 years of age at diagnosis. Half of the children were treated on a standard/high risk protocol. The majority of patients were treated with a chemotherapy only protocol (88%), which included prednisone, vincristine, and high dose intravenous methotrexate. 12% percent of participants were treated with cranial radiation, while all received triple intrathecal chemotherapy with methotrexate, hydrocortisone and cytarabine.

Full criteria for any subtype of ADHD (i.e. a sufficient number of symptoms that occur in multiple settings and that significantly impair functioning) was met by 10.5% of survivors, only slightly higher than the US national rate of 7.1% for children aged 6–11 years and 9.6% for children 12–17 years of age.[32] This 10.5% rate is not substantially different than the 9.8% rate found for children of non-Hispanic white ethnicity, the ethnicity of the majority of ALL survivors. 8.7% of survivors met criteria for the Inattentive subtype, 0.6% for the Hyperactive/Impulsive subtype, and 1.2% for the combined subtype. Frequent pervasive symptoms were reported by 36.6% of survivors, and 25.5% reported that symptoms impaired functioning. Table II presents frequencies for each of the 18 symptoms within the criteria for the diagnosis of ADHD. As shown, 32% of the ALL survivors reported significant symptoms of distractibility, while 22% reported being forgetful in daily activities. Although 32% of the survivors reported frequent fidgeting, few reported overt symptoms of hyperactivity (e.g. difficulty remaining seated in 8%; inappropriately running or climbing excessively in 6%) or symptoms of impulsivity (e.g. blurting out answers before question is completed in 9%; difficulty waiting turns in 9%). Only two survivors were using stimulant medication at the time of the evaluation, one of which met full criteria for ADHD. Interestingly, when asked about prior diagnoses and medication use, 17% of ALL survivors reported being previously diagnosed with ADHD, while 20% had previously taken stimulant medication, nearly twice the level that met the current criteria.

Given the relatively low frequency of hyperactive/impulsive symptoms of ADHD, associations between symptoms and demographic and treatment-related factors were examined for inattention and hyperactive/impulsive symptoms separately (Table III). Similar rates of ADHD symptoms were reported by male (14.6%) and female (15.3%) survivors, with no difference in levels of inattentive (symptom count mean [SD] for males = 1.8 [2.66], females = 1.8 [2.68], $p > 0.70$) or hyperactive/impulsive symptoms (mean [SD] for males = 1.2 [1.70], females = 1.2 [1.84], $p > 0.50$). Although trends appeared to emerge for several variables, symptoms of inattention or hyperactivity/impulsivity were not associated with age at diagnosis. Cranial radiation therapy (CRT) was associated with the number of ADHD symptoms. Survivors with a history of CRT displayed significantly more symptoms of inattention than survivors who were not treated with CRT (mean [SD] = 3.6 [3.19] for CRT group vs. 1.6 [2.40] for non-CRT group, $p=0.0006$).

The presence of leukoencephalopathy was not significantly related to the presence of ADHD symptoms ($p=0.37$; Table III). By contrast, impaired performance on an anti-saccade task, suggesting reduced integrity of frontal lobe functions, was significantly ($p = 0.0004$) related to more symptoms of inattention (mean [SD] = 3.4 [3.29], versus mean = 1.4 [2.41] for survivors with normal anti-saccade task; Table III).

DISCUSSION

The results of the current study demonstrate a similar rate of symptoms of ADHD in survivors of childhood ALL when compared to the rate in the general population, with 10.5% of the survivors reporting pervasive symptoms that significantly impact functioning and, thus, meeting full criteria for ADHD. Although the rate of hyperactive/impulsive symptoms was remarkably low, 8.7% of survivors did meet criteria for the Inattentive subtype, which is higher than expected. [17,33] Furthermore, 25.5% of the entire sample reported symptoms that impair function, albeit the number of symptoms was fewer than that required for the diagnosis of ADHD. This discrepancy between the number of symptoms and degree of impairment may suggest that the phenotype seen in ALL survivors is not fully captured by the standard DSM-IV criteria for ADHD. Previous literature suggests that ALL survivors are at significant risk for deficits in processing speed, [2,13] which are not included as standard symptoms of ADHD. The pattern of ADHD reported in the developmental literature frequently includes symptoms of hyperactivity and impulsive behaviors.[34] However, the symptom pattern in ALL survivors was focused more on inattention. In addition, the rate of developmental ADHD is reported to be more frequent in boys compared to girls.[32] However, we found no difference in the rate between sexes. This difference in symptom pattern and sex ratios may suggest that the phenotype seen in survivors of ALL is significantly different from that seen in developmental ADHD. Thus, an alternative profile of neurocognitive impairment may better capture the phenotypic pattern characteristic of ALL survivors.

An additional difficulty in the application of the ADHD syndrome to the phenotype seen in ALL survivors is age of onset. The DSM-IV requires that symptoms occur prior to age seven years.[17] However, many survivors of ALL were diagnosed and treated after this age cut-off. Furthermore, the onset of symptoms in ALL survivors is often delayed until years after treatment completion.

The discovered associations between ADHD symptoms and salient clinical variables suggest attention problems in ALL survivors are likely related to brain pathology, rather than environmental factors. Patients treated with CRT were more likely to display symptoms of inattention than those patients with no history of CRT treatment. Furthermore, those patients who displayed impairment on an anti-saccade task displayed significantly more symptoms

of inattention. The active inhibition required during anti-saccades has been associated with functional magnetic resonance imaging (fMRI) activation in frontal lobe regions.[28]. Impaired anti-saccades have been reported in patients with overt brain abnormalities, particularly abnormalities in frontostriatal circuits.[35,36] Leukoencephalopathy in frontostriatal regions have been associated with attention problems in ALL survivors.[14,16] However, these findings were based on direct neuropsychological performance testing, which was partially dependent on processing speed, and not behavioral observations. The measures of attention problems in the current study are limited to observable symptoms and do not include symptoms of impaired processing speed.

An unexpected outcome of the current study was the relatively high rate of reported diagnosis of ADHD and use of stimulant medication by survivors of childhood ALL. Seventeen percent of the survivors reported being previously diagnosed with ADHD, and 20% reported taking a stimulant medication in the past. However, only 10.5% met full diagnostic criteria for ADHD. This discrepancy may be related to enrollment of a proportion of participants on a prior institutional protocol examining the efficacy of stimulant medication on attention problems in survivors of ALL and central nervous system tumors. Although the prior study did not formerly assess or diagnosis survivors with ADHD, 50.9% of the participants went through a cognitive and behavioral screening evaluation and 9.3% participated in an extended medication trial (none of the patients were currently enrolled in this trial). Experience in this earlier protocol likely influenced report of prior diagnosis and stimulant use. Still, the 20% rate of reported prior stimulant medication use suggests that either formal diagnostic criteria are not being used in this patient population, or that the stimulant medications are being used to treat partial or different symptoms within the survivor group.

If the attention problem phenotype in survivors of ALL is substantially different from the behavioral syndrome of developmental ADHD, treatment options may also need to differ. Recent pharmacologic attempts at interventions for attention problems in survivors of pediatric ALL have employed medications and strategies with demonstrated efficacy in developmental ADHD (i.e. methylphenidate). These psychostimulant trials have demonstrated only mild improvement in a subset of patients. For example, in a large randomized, double-blind, crossover trial with methylphenidate, only 45% of the sample demonstrated a positive medication response,[37] a substantially lower response rate than that seen in developmental ADHD.[38,39] This reduced efficacy may, in part, be related to the unique phenotype seen in survivors of ALL. In addition, the fact that only two of the 161 survivors (1.2%) were currently using stimulant medication supports the conclusion that alternative treatment options are needed to address these problems. Clearly more research to better characterize this phenotype is needed to enhance specificity and efficacy of treatment.

The presence of ADHD in the general population appears heavily influenced by genetic variation.[40,41] Although limited research also suggests a genetic predisposition for attention problems in survivors of childhood ALL,[7] the current evidence points to different genetic pathways. Clearly, this is another area that requires further investigation.

The current investigation has several limitations. Although the sample size is relatively large, the study did not capture the entire cohort of eligible survivors at the institution. Although recruited survivors did not differ from non-recruited survivors on key demographic and treatment variables, there may be differences in other variables not analyzed. An additional limitation to the current study was the lack of inclusion of direct neurocognitive assessment of the survivors. Such assessment would have provided an opportunity to compare objective attention deficits with the subjective reports. Such an investigation is currently underway at our institution.

A significant proportion of survivors of childhood ALL are identified as having attention problems, albeit not meeting the full criteria for ADHD. The phenotype of attention problems in ALL survivors appears to differ from that seen in developmental ADHD. Few survivors demonstrate significant hyperactivity/impulsivity, while roughly 25% are reported to demonstrate functional impairment in daily activities. Recent research has described deficits in processing speed, mental flexibility, and cognitive efficiency, with relatively good behavioral and emotional functioning.[2,42–44] As such, we recommend focusing on a phenotype in ALL survivors that is comprised of neurocognitive deficits, including poor cognitive efficiency and executive dysfunction. Furthermore, we believe these deficits will manifest more readily through impaired performance rather than behavioral disruption. Given this pattern, survivors of childhood ALL are likely to require different treatments compared to those commonly employed with ADHD.

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Table I

Comparison of patient and treatment characteristics between participants and non-participants

	Participants		Non-Participants		
	N (161)	%	N (271)	%	p-value
Sex					0.89
Male	72	44.7	123	45.4	
Female	89	55.3	148	54.6	
Age at Diagnosis					0.99
<1 year	5	3.1	8	3.0	
1–10 years	129	80.1	218	80.4	
>10 years	27	16.8	45	16.6	
Risk Group					0.53
Low	66	41.0	107	39.5	
Standard/High	92	57.1	162	59.8	
Immunophenotype					0.94
B lineage	141	87.6	237	87.4	
T Lineage	20	12.4	33	12.2	
Mixed	0	0.0	1	0.4	
Chemotherapy Treatment					
Vincristine	160	99.4	267	98.5	0.42
High Dose Methotrexate	126	78.3	199	73.4	0.26
Intrathecal Methotrexate	161	100	271	100	1.00
Prednisone	155	96.3	261	96.3	0.98
Dexamethasone	34	21.1	46	17.0	0.28
Cranial Radiation					0.29
Yes	19	11.8	42	15.5	
No	142	88.2	229	84.5	

Table II

Frequency and severity of ADHD symptoms in survivors of childhood ALL

	Severity Rating (n)				
Inattentive Symptoms	**Never**	**Occasionally**	**Often**	**Very Often**	**% Impaired**
Fails to give close attention to details or makes careless mistakes in school, work of other activities	68	62	20	11	19%
Difficulty sustaining attention in tasks or play	88	42	18	13	19%
Does not seem to listen when spoken to directly	77	58	13	12	16%
Does not follow through on instructions and fails to finish school work, chores, or duties in work place	89	44	13	15	17%
Difficulty organizing tasks and activities	95	33	18	15	20%
Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	83	39	24	15	24%
Loses things necessary for tasks or activities	101	40	13	7	12%
Easily distracted by extraneous stimuli	64	45	25	26	32%
Forgetful in daily activities	77	49	19	16	22%
Hyperactive/Impulsive Symptoms	**Never**	**Occasionally**	**Often**	**Very Often**	**% Impaired**
Fidgets with hands or feet or squirms in seat	59	50	29	23	32%
Leaves seat in classroom or in other situations where remaining seated is expected	132	20	6	3	6%
Runs around or climbs excessively in situations in which it is inappropriate	130	18	4	9	8%
Has difficulty playing or engaging in leisure activities quietly	145	9	5	2	4%
Is “on the go” or often acts as if “driven by a motor”	106	28	17	10	17%
Talks excessively	93	34	15	19	21%
Blurts out answers before questions have been completed	107	38	8	7	9%
Has difficulty awaiting turn	126	20	11	4	9%
Interrupts or intrudes on others	101	43	9	8	11%
Pervasiveness of Symptoms	**Never**	**Occasionally**	**Often**	**Very Often**	**% Impaired**
Most of the symptoms are present at home and school (or work)	67	35	29	30	37%
Functional impact	**Yes**	**No**			
Symptoms of attention deficit, impulsivity, or hyperactivity impair social, school, or work functioning	41	120			

Note: %Impaired defined as those who report “Often” or “Very Often” experiencing symptoms.

Table III

Mean number of symptoms of ADD and ADHD

		Inattention			Hyperactive/Impulsive		
	n	Mean	(SD)	p value	Mean	(SD)	p value
Sex				0.70			0.54
Male	89	1.8	2.66		1.2	1.70	
Female	72	1.8	2.68		1.2	1.84	
Age at Diagnosis				0.19			0.15
< 4 year old	82	2.1	2.78		1.2	1.98	
≥ 4 years old	79	1.5	2.53		1.2	1.51	
Cranial Radiation Therapy				0.0006			0.41
No	142	1.6	2.50		1.2	1.77	
Yes	19	3.6	3.19		1.3	1.73	
Leukoencephalopathy				0.37			0.77
No	112	1.6	2.40		1.2	1.66	
Yes	39	2.4	3.15		1.3	2.14	
Sequential Hand Movement				0.09			0.11
Normal	94	1.4	2.41		1.0	1.54	
Impaired	51	2.3	2.94		1.5	1.96	
Anti-saccade Task				0.0004			0.10
Normal	122	1.4	2.41		1.1	1.74	
Impaired	27	3.4	3.29		1.5	1.81	