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Behavioral Symptoms and Psychiatric Disorders in Child and Adolescent Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia Treated with Chemotherapy Only

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Abstract

Background—Prevalence of emotional, behavioral and psychiatric outcomes in child and adolescent survivors of childhood acute lymphoblastic leukemia (ALL) treated on a chemotherapy-only protocol were not well defined.

Methods—Self- and parent-reported emotional and behavioral symptoms were assessed for 161 survivors of childhood ALL (51.0% female; mean [SD] age 12.1[2.6] years; 7.5[1.6] years post-diagnosis). Age- and sex-adjusted scores were calculated for standardized measures, and compared to 90th percentile of norms. Frequencies of survivor psychiatric disorders from structured diagnostic interviews with parents were compared to the general population. Parent emotional distress and posttraumatic stress symptoms were assessed. Associations between child symptoms/disorders and parent distress were examined with log-binomial models, adjusting for highest parent education.

Results—Compared to population expectations (10%), more survivors self-reported symptoms of inattention (27.9; 95% CI 21.0-35.7%), hyperactivity/impulsivity (26.0%; CI 19.2-33.6%), and oppositional-defiant behavior (20.1%; CI 14.1-27.3%). Parents reported survivors with more symptoms of inattention (23.6%; CI 17.2-31.0%), higher frequencies of Obsessive-Compulsive Disorder (10.3% vs. 2%) and Oppositional Defiant Disorder (16.0% vs. 9.5%), but not Attention-Deficit/Hyperactivity Disorder (7.1% vs 7.8%) or Generalized Anxiety Disorder (3.2% vs. 4.1%),

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compared to national norms. Parent-report of child anxiety disorders was associated with parent self-reported emotional distress, but not survivor self-report of anxiety.

Conclusion—A significant minority of survivors have long-term psychiatric morbidity, multi-informant assessment is important to understand these symptom profiles and to inform selection of appropriate interventions. Interventions targeting inattention and oppositional behavior in children and emotional distress in parents are warranted in families with survivors who display behavioral problems.

Keywords

cancer; oncology; childhood ALL; chemotherapy-only protocol; long-term survivor; behavior symptoms; psychiatric disorder

Introduction

Some adolescent long-term survivors of childhood acute lymphoblastic leukemia (ALL) experience psychosocial and behavioral problems, including symptoms of anxiety, depression, inattention, and antisocial behavior(1) either in isolation or as clusters of behavioral and emotional symptoms.(2, 3) Long-term survivors of childhood ALL treated with only chemotherapy demonstrate higher rates of headstrong behavior, inattention-hyperactivity (related to cognitive problems), social withdrawal and learning problems compared to healthy siblings, with higher risk of inattention-hyperactivity symptoms associated with higher cumulative doses of intravenous methotrexate.(4) Although the rate of Attention-Deficit/Hyperactivity Disorder (ADHD) appears comparable to the general population, a quarter of survivors report an adverse impact of behavioral symptoms on functional impairment.(5) There is evidence to suggest more emotional and behavioral symptoms in survivors of childhood ALL compared to the general population, however, the prevalence and severity of clinically diagnosed psychiatric disorders have not been well characterized in this population.

Studies that evaluate the presence of emotional or behavioral morbidities typically rely on self-report or proxy report of symptoms. This approach involves rating individual behaviors that cluster in symptom domains such as inattention, hyperactivity/impulsivity, depression and anxiety. However, the presence of symptoms alone may not be sufficient to warrant a formal diagnosis or treatment of psychiatric disorders. The gold standard for systematic assessment of psychiatric disorders involves the use of structured diagnostic interviews.(6) For example, a rating scale may provide a norm-referenced level of inattentive behavior, whereas the clinical diagnosis of ADHD requires not only the presence of sufficient symptoms, but also a minimum age at symptom onset, minimum symptom duration, evidence of clinically significant impairment in social, academic or occupational functioning, as well as differential diagnosis of conditions with overlapping symptoms (e.g. learning disability, anxiety disorders).(7) This formal diagnostic process for psychiatric disorders has not been regularly utilized among long-term survivors of childhood ALL.

There have been inconsistent reports pertaining to emotional distress in parents of survivors of childhood cancer,(8) Most parents of survivors of ALL treated on chemotherapy-only

protocols do not have elevated symptoms of anxiety, depression or post-traumatic stress symptoms (PTSS); however subgroups of parents do report substantial symptoms of psychological distress or PTSS.(8, 9) Furthermore, emotional distress such as post-traumatic stress symptoms (PTSS) can persist many years following the completion of therapy.(10) Parental distress has been associated with their report of emotional symptoms in child survivors of ALL, although it is unclear whether this distress impacts the child's emotional or behavioral symptoms.(9) The association between parental emotional distress or PTSS and behavioral problems in childhood cancer survivors requires further investigation.

The objectives of this study are (1) to examine the prevalence and pattern of parent-reported and self-reported behavioral symptoms in long-term survivors of childhood ALL; (2) to examine the prevalence of psychiatric disorders, diagnosed through structured diagnostic interviews; (3) to evaluate the impact of parent self-reported emotional distress and PTSS on report of child behavioral symptoms and psychiatric disorders; and (4) to evaluate the impact of treatment exposure on report of child behavioral symptoms and psychiatric disorders as well as parent self-reported emotional distress and PTSS.

Method

Patients

The institutional review board at St. Jude Children's Research Hospital approved the research protocol, and informed consent/assent was obtained from all parents and participants, as appropriate.

From 2000 to 2010, 408 children with ALL were treated at St. Jude Children's Research Hospital (SJCRH) on the Total Therapy XV protocol (ClinicalTrials.gov, NCT00137111). (11) To be eligible for long-term follow-up assessment of behavioral, emotional and psychiatric outcomes, survivors must be more than five years from diagnosis, between the age of 8 and 17 years at long-term follow-up and proficient in English. Survivors were excluded if they developed relapse or a secondary cancer that required cranial radiation or additional chemotherapy, had a pre-existing non-cancer-related neurodevelopmental or genetic disorder associated with functional impairment, or had a subsequent brain injury unrelated to their cancer.

All survivors were previously treated with high-dose intravenous methotrexate (HDMTX), triple intrathecal therapy (methotrexate, hydrocortisone, cytarabine), and oral dexamethasone, in addition to other chemotherapeutic agents. Children in the low-risk and standard-risk arms were treated with 2.5 gm/m² and 5 gm/m² per dose of HDMTX, respectively, for four doses. Exposures to HDMTX were measured as previously described. (12) Blood samples were drawn before HDMTX infusion and at six, 23, and 42 hours following the start of each HDMTX course. Exposures were quantified as area under the curve (AUC). Leucovorin rescue (10 to 15 mg/m²) was started 42 hours after HDMTX and repeated every six hours for a total of five doses. Prophylactic cranial radiation was not administered to any patient, regardless of presenting features, including the presence of CNS leukemia at diagnosis.

Behavior Symptom Rating and Diagnostic Interviews

Self-reported child behavioral symptoms (Conners' Rating Scale, 3rd edition(13)) and parent-report of child behavioral and emotional symptoms (Behavior Assessment System for Children [BASC-2](14)) were collected during the same visit. The Conners includes specific questions to evaluate symptoms of inattention, hyperactivity/impulsivity, learning problems, anxiety, depression, defiance/aggression, and symptom profiles consistent with DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) hyperactive Impulsive type and inattentive type, conduct disorder, and Oppositional Defiant Disorder(13). The BASC-2 evaluates symptoms of hyperactivity, aggression, conduct problems, anxiety, depression, somatization, atypicality, withdrawal, attention problems, adaptability, social interaction, leadership, and study skills.(14) Diagnostic Interview for Children and Adolescents (DICA-IV)(15) to systematically evaluates psychiatric disorders based on DSM-IV diagnostic criteria for children. The DICA is a semi-structured interview conducted by a clinician, and was completed with only parents in the current study.

Parent Emotional Distress/PTSS

Parent emotional distress was assessed using the Brief Symptom Inventory 18 (BSI-18)(16), which includes symptoms of depression, anxiety, and somatic complaints. Parent PTSS was evaluated using the Impact of Event Scale-Revised (IES-R)(17) and levels of stress were calculated for three subscales (thought intrusions, avoidance, and hyperarousal)using symptom raw scores. Parents' education level in years was used as a covariate in analyses involving parent report.

Statistical Analysis

Descriptive statistics for demographic and clinical variables were summarized and compared between participants and non-participants by using two-sample t-test for continuous variables and Chi-Square test for categorical variables. Age- and sex-adjusted standard scores were calculated for both self- and parent-report of child behavioral symptoms, and sex-adjusted standard scores were calculated for parent self-reported emotional distress. For child symptoms, impairment of Adaptability, Social Skills, Leadership, Activities of Daily Living, and Functional Communication was defined as 10th percentile of national normative data (T-score ≤ 37); impairment of other outcomes were defined as a score above the 90th percentile compared to normative data (T-score ≥ 63). For child mental health conditions, the proportions of children meeting diagnostic criteria on the DICA were compared to lifetime prevalence estimate of DSM-IV disorders in the National Comorbidity Survey (NCS-R) sample for age 18-29 years.(18) One-sample binomial tests were applied to compare the observed to the expected impairment rate in the general population. All p-values were adjusted for multiple testing by controlling the false discovery rate using SAS MULTTEST procedure. Spearman correlation was used to examine associations between self-reported and parent-reported symptom scores, as well as child's self-reported anxiety and depression total raw scores with parents' self-reported anxiety and depression scores.

Multivariable log-binomial regression analyses were conducted to independently test associations between each treatment exposure (HDMTX, number of intrathecal therapy doses, and cumulative dose of dexamethasone) and outcomes of child behavioral symptoms

and mental health conditions, adjusted for age at diagnosis. Similar analyses were conducted to test associations between parent emotional distress (anxiety, depression and somatization) or the number of PTSS symptoms reported (avoidance, hyperarousal, and intrusion) with parent- and self-reported child behavior symptoms, with adjustment for highest parent education. Relative Risks (RR) and 95% confidence intervals (CI) are reported from all analyses. General linear model (GLM) was used to identify associations between treatment exposures and parent self-reported emotional distress and number of PTSS symptoms. All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC).

Results

A total of 236 survivors were eligible for follow-up and 161 (68.2%) participated (Appendix Figure 1). Demographic, clinical and treatment characteristics of survivors and parents are provided in Table 1. 51% were female, 75% were white, mean age at diagnosis was 4.6 (Standard Deviation, SD 2.4) years, average follow-up time was 7.5 (SD 1.6) years and 81% of primary respondents were mothers. There were no significant differences between participants and non-participants on demographics or treatment characteristics (Table 1). Compared to an expected impairment proportion of 10%, a significantly larger proportion of survivors reported symptoms of inattention, hyperactivity/impulsivity, learning problems, ADHD hyperactive-impulsive type, ADHD inattentive type, and Oppositional Defiant Disorder, with impairment proportions ranging from 20-29% (Table 2). Parent report of survivor behavior demonstrated significantly more impairment in the areas of depression, atypicality, attention problems and activities of daily living (Table 2, range 17-26%). Results from the structured diagnostic interviews with parents demonstrated that survivors have higher rates for Obsessive Compulsive Disorder (10.3 vs. 2%) and Oppositional Defiant Disorder (16.0 vs. 9.5%) but lower rates of Conduct Disorder (0.6 vs. 10.9%) and Major Depressive Disorder (1.3 vs. 15.4%) compared to lifetime rates in the general population of adolescents/young adults. Prevalence of ADHD among survivors (7.1%) was comparable to national normative data (8.1%). Chemotherapy treatment was not associated with any of the child and parent outcomes (Appendix Table 2).

Survivors' self-report of inattention, hyperactivity/impulsivity, and defiance/aggression symptoms was significantly correlated with parent report of child attention problems, hyperactivity, and aggression/conduct problems, respectively, with all pairwise Spearman correlation coefficients ranging from 0.32 to 0.44 and all p -values < 0.001 (Appendix Table 3). However, survivors' self-reported anxiety ($r=0.25$) and depression ($r=0.17$) symptoms were weakly correlated with parent report of these survivor symptoms. Survivors' self-reported symptoms of mental health conditions (i.e., ADHD hyperactive-impulsive type, ADHD inattentive type, Conduct Disorder and Oppositional Defiant Disorder) were significantly associated with parent report of survivor mental health disorder (Appendix Table 3). Generalized Anxiety Disorder and Obsessive-Compulsive Disorder are psychiatric disorders associated with significant anxiety, (7, 19) these conditions were not associated with survivors' self-report of anxiety symptoms (Figure 1).

The majority of parents did not self-report elevated symptoms of emotional distress or posttraumatic stress symptoms (Appendix Table 1). Parent self-reported anxiety, depression

and PTSS showed significantly higher risk for parent report of survivor anxiety, atypicality, Generalized Anxiety Disorder and Obsessive Compulsive Disorder (Figure 2 and Appendix Figure 2).

Discussion

In the current study of child and adolescent long-term survivors of childhood ALL treated on a contemporary chemotherapy-only protocol, a significantly higher prevalence of **attention** problems were reported by both survivors ("Inattention" on Conner's) and parents ("Attention Problems" on BASC-2) compared to national normative data. In contrast, the prevalence of ADHD, based on a structured diagnostic interview, did not differ from the general population. Survivors also reported a significantly higher frequency of learning problems, which may be associated with attention problems. Compared to national normative data, survivors reported significantly higher symptoms of oppositional behavior and this behavior was consistent with Oppositional Defiant Disorder ascertained from structured diagnostic interviews with parents. Parents identified comparable prevalence of Generalized Anxiety Disorder, but higher Obsessive Compulsive Disorder in survivors relative to national data; however, these conditions were more strongly associated with parents' self-reported distress than with the survivors' self-reported anxiety. Parents reported lower Conduct Disorder and Major Depressive Disorder in survivors compared to national norms.

Agreement was demonstrated between diagnosis of Oppositional Defiant Disorder based on structured diagnostic interview, and survivors' report of symptoms of Oppositional Defiant Disorder. This disorder is characterized by children showing a persistent pattern of anger and irritable mood or argumentative and defiant behavior towards authority figures such as parents or teachers.(7) As one of the most commonly diagnosed psychiatric disorders in childhood and adolescence, the behavior can negatively impact children's social, academic or educational functioning.(20) We have previously demonstrated that survivors of ALL have higher frequency of executive dysfunction, including working memory, cognitive flexibility and organization skills. (21),(22) These cognitive abilities are important for children to comply with parental demands, and deficits may contribute to negative interactions with parents that are perceived as defiant behaviors.(20) Executive dysfunction has also been shown to be associated with emotional problems in adolescent survivors of childhood ALL,(23) which may contribute to parent-child conflict.

Survivor-report of symptoms of inattention was consistent with parent-report of survivor attention problems. Attention problems have been reported in a large cohort of adult survivor of ALL.(21) In that study, long-term survivors treated with chemotherapy only demonstrated significantly worse performance on direct testing of sustained attention compared to normative data.(22) Childhood Cancer Survivor Study investigators observed that parents reported a higher frequency of inattention/hyperactivity among adolescent survivors of ALL survivors compared to siblings.(4) Although more attention problems were noted in the current cohort, the rate of clinical diagnosis of ADHD was similar to the general population. Thus, the attention deficits likely reflect neurocognitive and learning problems rather than a pattern consistent with developmental ADHD.(5, 24)

Parents reported comparable prevalence for Generalized Anxiety Disorder, but increased Obsessive Compulsive Disorder compared to population data. Interestingly, the presence of the disorders identified by parents was not associated with survivors' self-report of anxiety. Instead, it was associated with parent self-report of emotional distress and PTSS. Previous studies have observed that parents of childhood cancer survivors experience higher psychological distress compared to the general population.(8) Parents' emotional distress may promote a negative bias towards perceiving behavioral and emotional problems in their children. Maternal self-reported anxiety, stress, and depression have been identified to impact parent-report of child emotional and behavior problems in the general non-cancer population.(25) Although parents did not demonstrate higher emotional distress or PTSS compared to normative data,(9) which may be attributed to the strong social and psychological support they received during and after therapy completion, those parents who did demonstrate distress were more likely to report distress in their children.

The finding of lower rates of Conduct Disorder in survivors is unexpected, but not surprising. Risk of Conduct Disorder is higher in children with ADHD,(26, 27) and we did not find higher prevalence of ADHD in survivors. Further, some research shows positive family outcomes following treatment for childhood cancer.(8) Recent studies have also shown that childhood cancer survivors who are at higher risk for neurocognitive impairment, as are the survivors in this sample, do not show significant symptoms of aggressive behavioral problems.(28)

We did not find associations between chemotherapy treatment and any child self- or parent-reported symptoms or psychiatric disorders. Similar findings were reported from the Children's Cancer Group (CCG protocol 105).(29) and behavioral outcomes in long-term survivors of childhood ALL from the Netherlands.(30) A lack of association between chemotherapy treatment and a child's behavior symptoms and psychiatric disorders suggests that the cancer experience (e.g., recurrent hospitalizations, painful procedures) and not the treatment itself may contribute to the development of the behavioral and emotional problems.(31, 32)

Study Limitations

This study should be viewed in light of several limitations. First, there was no healthy control group included in this study. However, we have a relatively large sample of childhood ALL survivors, self- and parent-reported behavior symptoms were evaluated using two widely used rating scales,(7) and T-scores were generated from national normative data with age- and sex- adjustment, which to some extent mitigates the concern of not having a healthy control group. Future study design should consider including age- sex- matched community control so that we may control impacts of some other potential confounding factors in analysis. Second, the DICA was conducted only with parents and not survivors. We selected this method as, in our experience, children younger than 12 are not as reliable in their report of mental health problems and we desired a single respondent format for our sample of 8-17.9 year-old survivors. Also, survivors of childhood ALL are at risk for neurocognitive impairment and it is unclear what the impact of such impairment might have on the semi-structured interview with the child. Third, there was no normative data available

for DICA, psychiatric diagnoses in the current study were determined with the DICA and referred to the lifetime prevalence estimate of DSM-IV disorders in the NCS-R sample for age 18-29 years (18) which should be a fair reference, it is safe to say the prevalence for age 8-17 years in general population should be less than these reference. Fourth, there was no pre-therapy testing of behavior symptoms or diagnosis, but such assessments are difficult to obtain in young children at the time of a cancer diagnosis. To account for this limitation we adjusted analyses for parent education, which should provide a reasonable surrogate for socioeconomic status.(33) Last, this is a single center study, potentially limiting generalization. Patients treated at St. Jude and during cancer survivorship have strong social and psychological support, in that the prevalence of symptoms and disorders could be underestimated comparing to other patients who are treated in clinics without such support.

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Appendix

Appendix Figure 1.
Consort Diagram

Appendix Figure 2. Association of Parent Posttraumatic Stress Symptoms with Self- and Parent-Reported Behavior Symptoms and Psychiatric Disorders

Relative Risk and 95% Confidence Interval for Parent Posttraumatic Stress Symptoms on Self- and Parent-Reported Behavior Symptoms.

Multiple regression analysis adjusted for parents' highest years of education.

Relative Risk and 95% Confidence Interval scale: per one more symptom reported according to Event Scale-Revised. Abbreviations: CRS-3, Conners' Rating Scale, 3rd edition; BASC-2, Behavior Assessment System for Children, 2nd edition; DICA-IV, Diagnostic Interview for Children and Adolescents IV.

Self-Reported Symptoms/Conditions (Conners' Rating Scale 3rd edition): Inattention, Hyperactivity/Impulsivity, Learning Problems, Defiance/Aggression, Family Relations, ADHD Hyperactive-Impulsive Type, ADHD Inattentive Type, Conduct Disorder and Oppositional Defiant Disorder. **Parent-Reported Symptoms** (Behavior Assessment System for Children BASC-2): Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Withdrawal, Attention Problems, Adaptability, Social Skills, Leadership, Activities of Daily Living and Functional Communication.

Parent-Reported Psychiatric Disorders (Diagnostic Interview for Children and Adolescents IV DICA-IV): ADHD Present, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder and Oppositional Defiant disorder.

Appendix Table 1

Summary Statistics for Parent Emotional Distress and Posttraumatic Stress Outcomes

	n	Mean (SD)
Emotional Distress [†]		
Anxiety	155	45.7 (9.6)
Depression	155	44.7 (7.3)
Somatization	155	44.9 (6.7)
Posttraumatic Stress Symptoms [‡]		
Avoidance	153	5.6 (6.0)
Hyperarousal	153	3.8 (5.2)
Intrusion	153	2.4 (3.9)

Abbreviations: SD, standard deviation

[†]Brief Symptom Inventory 18 (BSI-18): sex-adjusted T scores (mean=50, SD=10)[‡]Impact of Event Scale-Revised (IES-R): number of symptoms reported**Appendix Table 2**

Association of Chemotherapy Treatment Effect and Child and Parent Outcomes

	HDMTX AUC			Intrathecal therapy [†]			Oral dexamethasone		
Survivor Outcomes [‡]									
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Self-Reported Symptoms									
Inattention	0.98	0.96- 1.01	0.465	0.96	0.89- 1.03	0.56	0.92	0.85- 1.00	0.18
Hyperactivity/Impulsivity	1.01	0.99- 1.03	0.465	1.02	0.96- 1.09	0.71	0.99	0.89- 1.11	0.89
Learning Problems	1.01	0.99- 1.04	0.465	1.05	0.98- 1.12	0.56	1.07	0.94- 1.21	0.64
ADHD Hyperactive- Impulsive Type	1.01	0.99- 1.03	0.465	1.04	0.97- 1.11	0.56	1.02	0.91- 1.15	0.89
ADHD Inattentive Type	0.99	0.97- 1.02	0.53	0.99	0.92- 1.06	0.71	0.91	0.84- 0.99	0.12
Oppositional Defiant Disorder	0.99	0.96- 1.02	0.53	1.02	0.94- 1.10	0.71	0.98	0.86- 1.13	0.89
Parent-Reported Symptoms									
Depression	1	0.97- 1.03	0.91	1.01	0.93- 1.08	0.92	1.02	0.89- 1.17	0.95
Atypicality	0.99	0.96- 1.03	0.91	1.04	0.97- 1.12	0.92	1	0.87- 1.16	0.95
Attention Problems	1	0.98- 1.03	0.91	1	0.94- 1.07	0.92	0.95	0.85- 1.06	0.95
Activities of Daily Living	0.98	0.95- 1.01	0.6	0.98	0.92- 1.05	0.92	0.99	0.89- 1.10	0.95
Parent-Reported Psychiatric Disorders									
Generalized Anxiety Disorder	1	0.94- 1.06	0.95	0.84	0.63- 1.12	0.63	0.93	0.67- 1.28	0.66
Obsessive-Compulsive Disorder	1.03	0.99- 1.06	0.3	1.04	0.94- 1.16	0.63	1.18	0.95- 1.47	0.39
Oppositional-Defiant Disorder	0.98	0.94- 1.01	0.3	0.99	0.91- 1.08	0.84	0.94	0.81- 1.09	0.6
Parent Outcomes [§]									
	Est	SE	P	Est	SE	P	Est	SE	P
Emotional Distress									

	HDMTX AUC			Intrathecal therapy [†]			Oral dexamethasone		
Survivor Outcomes [‡]									
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Anxiety	0.027	0.014	0.14	0.051	0.041	0.33	0.046	0.06	0.66
Depression	0.011	0.01	0.41	0.042	0.031	0.33	0.025	0.046	0.66
Somatization	0.006	0.01	0.55	-0.003	0.029	0.92	0.019	0.043	0.66
Posttraumatic Stress Symptoms									
Avoidance	0.074	0.037	0.14	0.153	0.112	0.51	0.09	0.166	0.89
Hyperarousal	0.027	0.028	0.48	0.064	0.085	0.69	0.071	0.124	0.89
Intrusion	0.031	0.043	0.48	0.022	0.13	0.86	0.012	0.191	0.95

Abbreviations: RR, Relative Risk; 95% CI, 95% Confidence Interval; Est, Parameter Estimate; SE, Standard Error; HDMTX AUC, high dose IV methotrexate plasma concentration (area under curve [AUC]);

[†]Triple intrathecal therapy of MTX, hydrocortisone, plus cytarabine oral dexamethasone, oral dexamethasone cumulative dose per 100 mg/m² at 120 week.

P: P-value from multiple regression analysis adjust for age at diagnosis, with FDR adjustment

[‡]Relative Risk per 1 unit of HDMTX AUC increased, or 1 more intrathecal injection, or 100 mg/m² increase in oral dexamethasone

[§]BSI T-score or number of PTS symptoms per 1 unit of HDMTX AUC increased, or 1 intrathecal injection increased, or 100 mg/m² increase in oral dexamethasone

Appendix Table 3

Association of Self- Reported and Parent-Reported Child's Behavior Symptoms with Psychiatric Disorders

	Survivor-Reported Symptoms						
	Inattention [†]	Hyperactivity/Impulsivity [†]	Learning Problems [†]	Defiance/Aggression [†]	Family Relations [†]	Anxiety [‡]	Depression [‡]
Parent-Reported Symptoms [‡]	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Hyperactivity	0.31 (<0.0001)	0.41 (<0.0001)	0.26 (0.002)	0.34 (<0.0001)	0.25 (0.002)	0.19 (0.020)	0.19 (0.022)
Aggression	0.31 (<0.0001)	0.30 (<0.0001)	0.15 (0.063)	0.32 (<0.0001)	0.20 (0.016)	0.13 (0.124)	0.12 (0.145)
Conduct Problems	0.31 (<0.0001)	0.35 (<0.0001)	0.17 (0.042)	0.41 (<0.0001)	0.30 (<0.0001)	0.21 (0.010)	0.23 (0.005)
Anxiety	0.12 (0.145)	0.10 (0.222)	0.15 (0.070)	0.01 (0.856)	-0.09 (0.270)	0.25 (0.002)	-0.10 (0.217)
Depression	0.32 (<0.0001)	0.20 (0.015)	0.24 (0.003)	0.24 (0.004)	0.14 (0.096)	0.26 (0.001)	0.17 (0.037)
Somatization	0.08 (0.324)	-0.02 (0.772)	0.04 (0.622)	0.01 (0.913)	-0.03 (0.698)	0.18 (0.023)	0.01 (0.870)
Atypicality	0.31 (<0.0001)	0.24 (0.004)	0.19 (0.018)	0.32 (<0.0001)	0.24 (0.003)	0.24 (0.004)	0.17 (0.041)
Withdrawal	0.21 (0.010)	0.08 (0.324)	0.09 (0.256)	0.20 (0.014)	0.10 (0.222)	0.19 (0.018)	0.10 (0.232)
Attention Problems	0.44 (<0.0001)	0.35 (<0.0001)	0.34 (<0.0001)	0.31 (<0.0001)	0.32 (<0.0001)	0.25 (0.002)	0.26 (0.001)
Adaptability	-0.26 (0.002)	-0.25 (0.002)	-0.16 (0.045)	-0.38 (<0.0001)	-0.23 (0.004)	-0.25 (0.002)	-0.12 (0.125)
Social Skills	-0.17 (0.041)	-0.13 (0.119)	-0.01 (0.863)	-0.25 (0.002)	-0.18 (0.029)	-0.08 (0.354)	-0.09 (0.279)
Leadership	-0.26 (0.001)	-0.19 (0.019)	-0.21 (0.009)	-0.33 (<0.0001)	-0.16 (0.047)	-0.12 (0.155)	-0.16 (0.052)
Activities of Daily Living	-0.33 (<0.0001)	-0.26 (0.002)	-0.27 (0.001)	-0.31 (<0.0001)	-0.30 (<0.0001)	-0.15 (0.065)	-0.22 (0.006)
Functional Communication	-0.27 (0.001)	-0.21 (0.010)	-0.29 (<0.0001)	-0.30 (<0.0001)	-0.24 (0.003)	-0.18 (0.029)	-0.16 (0.055)
	Self-Reported Symptoms of Conditions						
	ADHD Hyperactive-Impulsive Type [§]	ADHD Inattentive Type [§]	Conduct Disorder [§]	Oppositional Defiant Disorder [§]			
Parent-Reported Disorders [¶]	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)			

	Survivor-Reported Symptoms						
	Inattention [†]	Hyperactivity/ Impulsivity [†]	Learning Problems [†]	Defiance/ Aggression [†]	Family Relations [†]	Anxiety [‡]	Depression [‡]
ADHD	5.05 (1.27-20.10)	4.11 (1.03-16.44)	4.99 (1.31-18.94)	3.81 (1.01-14.37)			
Generalized Anxiety Disorder	1.01 (0.11- 9.41)	0.82 (0.09- 7.68)	8.31 (1.26-55.03)	1.27 (0.14-11.78)			
Obsessive-Compulsive Disorder	2.25 (0.84- 6.06)	1.36 (0.48- 3.82)	3.30 (1.17- 9.31)	1.57 (0.53- 4.67)			
Oppositional Defiant Disorder	1.51 (0.66- 3.46)	1.85 (0.84- 4.07)	3.32 (1.51- 7.34)	2.85 (1.32- 6.16)			

Abbreviations: r (p), Spearman Correlation Coefficient (p-value); RR, Relative Risk; 95% CI, 95% Confidence Interval.

ADHD, Attention-Deficit/Hyperactivity Disorder

[†] Age- and Sex-adjusted T scores (Mean=50, SD=10);

[‡] Symptom raw scores;

[§] Impaired Symptom (T-score ≥ 63);

[¶] Child psychiatric disorders meeting clinical criteria.

Note: r (p) with bold fonts in the top part of the table indicate the suggested the outcomes with same measures between self and parent reports.

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Clinical Implications

A significant minority of survivors exhibit significant symptoms of inattention and oppositional behavior based on agreement between child and parent report. In contrast to a previous report comparing survivors to siblings(4), treatment exposures were not associated with these symptoms among survivors compared to normative data, which suggests that the cancer experience itself may play a major role in the development of these symptoms and disorders. Further, parental emotional status appears to influence their perception and reporting of child outcomes. Our findings suggest that long-term adolescent survivors of ALL should be periodically screened for attention problems, oppositional behavior and anxiety disorders and that parents of survivors should be monitored for emotional distress. Preventative interventions targeting behavioral outcomes in pediatric patients with ALL and, when present, emotional distress in parents should be considered. Family therapy that includes both the parent and survivor may also be beneficial for those survivors with oppositional behavior.

Figure 1. Association between Self-Reported Anxiety Raw Score and Parent-Reported Child Anxiety Disorders

Box and Whiskers plot: Self-reported anxiety raw score (Mean and 95% CI) vs. parent-reported child Obsessive-Compulsive Disorder and Generalized Anxiety Disorder.

Figure 2. Relative Risk for Parent Emotional Distress on Self- and Parent- Reported Behavior Symptoms and Psychiatric Disorders

Multiple regression analysis adjust for parents' highest education level in years; Relative Risk and 95% Confidence Interval scale: per 0.5 SD of Parent Emotional Distress BSI T-score increased.

Self-Reported Symptoms/Conditions (Conners' Rating Scale 3rd edition): Inattention, Hyperactivity/Impulsivity, Learning Problems, Defiance/Aggression, Family Relations, ADHD Hyperactive-Impulsive Type, ADHD Inattentive Type, Conduct Disorder and Oppositional Defiant Disorder. **Parent-Reported Symptoms** (Behavior Assessment System for Children BASC-2): Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Withdrawal, Attention Problems, Adaptability, Social Skills, Leadership, Activities of Daily Living and Functional Communication.

Parent-Reported Psychiatric Disorders (Diagnostic Interview for Children and Adolescents IV DICA-IV): ADHD Present, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder and Oppositional Defiant disorder.

Table 1

Demographics and Treatment Characteristics

		Participants (total n=161)			Non-Participants (total n=75)			p
		No.	%	Mean (SD)	No.	%	Mean (SD)	
Demographics								
Sex	Female	82	50.9		37	19.3		
	Male	79	49.1		38	50.7		0.82
Race	White	120	74.5		58	77.3		
	Others	41	25.5		17	22.7		0.64
Age at valuation	Years	161		12.1 (2.6)				
Maternal education	Years	158		13.7 (2.5)				
Paternal education	Years	153		13.5 (3.1)				
Treatment characteristics								
Age at diagnosis	Years	161		4.6 (2.4)	75		5.5 (3.9)	0.07
Time since diagnosis	Years	161		7.5 (1.6)				
Risk Stratum	Low	110	68.3		44	58.7		
	Standard/High	51	31.7		31	41.3		0.13
HDMTX AUC	mg.hr/L	156		31.0 (11.6)	75		32.4 (11.5)	0.41
HDMTX cumulative dose	g/m ²	160		15.9 (5.1)	75		16.4 (5.3)	0.5
Intrathecal therapy [†]	No. counts	158		14.0 (3.8)	75		13.7 (4.5)	0.58
Oral dexamethasone	100 mg/m ²	157		11.2 (2.6)	66		11.3 (2.9)	0.77

Abbreviations: SD, standard deviation; Min, Max: minimum and maximum values HDMTX: High dose intravenous methotrexate; AUC area under the curve
[‡]Triple intrathecal therapy of MTX, hydrocortisone, plus cytarabine.

Table 2

Summary Statistics on Self-Reported and Parent-Reported Behavior Symptoms and Psychiatric Disorders (N=161)

	T-score	Impairment		
	Mean (SD)	n (%)	Exact 95% CL	P
Self-Reported Symptoms/Conditions				
Inattention	55.6 (13.9)	43 (27.9)	21.0-35.7	<0.0001
Hyperactivity/Impulsivity	55.9 (12.4)	40 (26.0)	19.2-33.6	<0.0001
Learning Problems	54.5 (11.3)	35 (22.7)	16.4-30.2	<0.0001
Defiance/Aggression	51.1 (11.3)	18 (11.7)	7.1-17.8	0.62
Family Relations	49.8 (9.5)	17 (11.0)	6.6-17.1	0.75
ADHD Hyperactive-Impulsive Type	54.9 (12.5)	38 (24.7)	18.1-32.3	<0.0001
ADHD Inattentive Type	56.1 (13.2)	45 (29.2)	22.2-37.1	<0.0001
Conduct Disorder	49.2 (10.4)	16 (10.4)	6.1-16.3	0.87
Oppositional Defiant Disorder	53.1 (11.8)	31 (20.1)	14.1-27.3	0.00004
Parent-Reported Symptoms				
Hyperactivity	50.4 (12.7)	24 (15.3)	10.0-21.9	0.054
Aggression	48.2 (10.1)	13 (8.3)	4.5-13.7	0.60
Conduct Problems	48.7 (10.9)	14 (9.0)	5.0-14.6	0.72
Anxiety	50.4 (12.4)	20 (12.7)	8.0-19.0	0.35
Depression	51.2 (12.0)	26 (16.6)	11.1-23.3	0.022
Somatization	50.9 (12.3)	24 (15.3)	10.0-21.9	0.054
Atypicality	50.5 (11.3)	28 (17.9)	12.3-24.9	0.004
Withdrawal	48.9 (10.3)	17 (10.8)	6.4-16.8	0.73
Attention Problems	53.3 (11.3)	37 (23.6)	17.2-31.0	<0.0001
Adaptability	50.5 (10.3)	18 (11.5)	6.9-17.5	0.63
Social Skills	48.8 (10.0)	24 (15.3)	10.0-21.9	0.054
Leadership	48.7 (10.1)	23 (14.7)	9.6-21.3	0.084
Activities of Daily Living	45.9 (10.6)	40 (25.5)	18.9-33.0	<0.0001
Functional Communication	48.8 (9.9)	21 (13.5)	8.5-19.8	0.23
Parent-Reported Psychiatric Disorders				
	Expected $\hat{\tau}$ (%)	n (%)	Exact 95% CL	P
ADHD Present	7.8	11 (7.1)	3.6-12.3	0.78
Conduct Disorder $\hat{\tau}$	10.9	1 (0.6)	0.0- 3.5	0.0001
Major Depressive disorder $\hat{\tau}$	15.4	2 (1.3)	0.2-4.6	<0.0001
Dysthymic	1.7	5 (3.2)	1.0-7.3	0.18
Generalized Anxiety Disorder	4.1	5 (3.2)	1.0- 7.3	0.63
Obsessive-Compulsive Disorder	2	16 (10.3)	6.0-16.2	<0.0001
Oppositional-Defiant Disorder	9.5	25 (16.0)	10.6-22.7	0.008

	T-score	Impairment		
	Mean (SD)	n (%)	Exact 95% CL	P
Panic Disorder	4.4	0 (0.0)	0.0- 2.3	0.11

T-score: Age- and Sex-adjusted T scores, mean=50, SD=10; Impairment for Adaptability, Social Skills, Leadership, Activities of Daily Living, and Functional Communication impairment was defined as 10th percentile of national norm (T-score 37); for other variables, impairment was defined as 90th of national normative data (T-score 63).

[†]Expected: lifetime prevalence estimate of DSM-IV disorders in the NCS-R sample for age 18-29 years, Kessler RC et al, 2005. P: p-value for two-sided, one sample Binomial test for p=0.1 with False Discovery Rate adjustment.

[‡]Conduct Disorder: Frequency of impairment is lower than national normative data.