Open Access Library Journal
2022, Volume 9, e9337
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Neuro-Cognitive Functions in ALL Childhood Cancer Survivors in NCI, Cairo University, Egypt

Menna Shamma[1], Ahmed Kamel[1], Doaa R. Ayoub[2], Mohamed H. Fawzy[1]

[1]Pediatric Oncology Department, NCI, Cairo University, Cairo, Egypt
[2]Psychiatry Department, Faculty of Medicine, Cairo University, Cairo, Egypt
Email: mennashamma@gmail.com

How to cite this paper: Shamma, M., Kamel, A., Ayoub, D.R. and Fawzy, M.H. (2022) Neuro-Cognitive Functions in ALL Childhood Cancer Survivors in NCI, Cairo University, Egypt. *Open Access Library Journal*, **9**: e9337.
https://doi.org/10.4236/oalib.1109337

Received: September 18, 2022
Accepted: October 21, 2022
Published: October 24, 2022

Abstract

Objective: Acute Lymphoblastic Leukemia (ALL) is one of the most common childhood malignancies, accounting for about 75% of all leukemias and a quarter all of childhood cancers, in this research we aimed at assessing neuro-cognitive consequences in children with Acute Lymphoblastic Leukemia who have been treated with chemotherapy. **Methods:** 95 children aged between 6 and 12 years old completed Wechsler Intelligence Scale for Children (WISC III). Sixty-one children were ALL survivors at the Pediatric Oncology Department, NCI, Cairo University compared to thirty-four were control group consisted of matching children from the same age group. Study patients have successfully accomplished their treatment protocol and were in complete remission during the evaluation for ≥ 2 years under follow up without relapse and no pre-diagnosis history of neuro-developmental disorder nor psychiatric disorders as evidenced by Child Behaviour Checklist (CBCL). **Results:** Subjects scored significantly below levels for their matched controls. The difference between patients and controls was significant ($p < 0.001$) for the following measures: Total IQ, Verbal IQ, Performance IQ scores, (84.8 ± 10 vs. 98.7 ± 10.3), (94.4 ± 13.5 vs. 110.1 ± 13.6) and (76.6 ± 10 vs. 85.5 ± 8.5) respectively. Sex was considered a risk factor where females performed worse than males in verbal IQ with significance (p-value = 0.045). **Conclusions:** Long-term sequels in neuro-cognitive functions were found in the chemotherapy only group, female patients were at higher risk than males; observed in the impairments of memory, attention, logical thinking and social knowledge.

Subject Areas

Pediatric Oncology, Pediatric Psychiatry

Keywords

Acute Lymphoblastic Leukemia, Neuro-Cognitive Functions, Child Behavior

Checklist, Chemotherapy, Wechsler Intelligence Scale

1. Introduction

Acute Lymphoblastic Leukaemia (ALL) is one of the most common childhood malignancies, accounting for about a quarter of all childhood malegnancies, with a peak incidence at the age of 3 - 4 years [1].

Current treatment commonly lasts for 24 - 30 months. Almost entirely all protocols include central nervous system prophylactic treatment to prevent relapse. Treatment is based mostly on complex multi-agent combinations of chemotherapies; the intensity of the therapy is determined according to risk groups, defined by graded risk for relapse and long-term sequel. Some very high-risk cases also involve the use of cranial radiation therapy (CRT) [2].

Central nervous system (CNS)-directed therapy is an integral part of ALL treatment. Prophylactic CNS-directed radiotherapy has been mostly abandoned due to its detrimental effects on brain development and intellectual functioning. In more current treatment protocols, intensified CNS-directed chemotherapy, with intravenous (IV) and intrathecal (IT) methotrexate (MTX) as major backbones, has replaced radiotherapy [3].

However, chemotherapy-based CNS-directed treatment may have a negative impact on cognitive functioning in ALL survivors as well, although likely to a lesser extent than radiotherapy [3].

Earlier studies that focused on treatment effects often reported fewer and only subtle deficits in the chemotherapy only groups as compared to survivors treated with CRT, while other studies have reported no significant cognitive differences between such groups [2].

Studies that have focused on both treatment and illness factors by including multiple samples (CRT treatment, chemotherapy only treatment, other illnesses such as non-central nervous system cancer and healthy controls) have shown a gradual effect on cognitive functions [2].

Recent research has concentrated on more specific cognitive abilities and ALL survivors have been reported to show deficits in several neuro-cognitive domains, such as processing speed, attention, executive functions, and working memory [3].

The lower scores on the Wechsler Intelligence Scale for Children as documented in the literature might reflect impairment of both global and/or specific neuro-cognitive abilities. In fact studies that focused on outcomes for specific cognitive functions have reported significant impairment in Verbal IQ, Performance IQ, attention, information processing, executive functions, psychomotor skills, as well as verbal visual memory [4] and learning difficulties. Specific impairment in non-verbal function and freedom from distractibility has been documented, but specific impairment of Verbal IQ has also been documented [1].

As brain development continues into early adulthood, long-term cognitive outcomes in ALL survivors may not become evident until years after completion of treatment. Until now, follow-up time in ALL survivors treated exclusively with chemotherapy has been limited, and thus, little is known about long-term neurocognitive functioning in ALL survivors who have lived for more than 10 years after their diagnosis [3].

The objective of this study was to evaluate cognitive consequences in childhood Acute Lymphoblastic Leukemia survivors at national cancer institute, Cairo University treated with chemotherapy and to evaluate correlation between cognitive functions and different variables such as: demographic, protocol given, duration of therapy, etc.

Statistical Analysis

Statistical analysis was done using IBM SPSS® Statistics version 22 [5] Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Pearson's Chi-square test was used to examine the relation between qualitative variables. All tests were two-tailed. A p-value < 0.05 was considered significant.

Sample size was calculated using G * Power program (University of Düsseldorf, Düsseldorf, Germany).

2. Methods

The present study consists of 61 children long-term survivors of childhood ALL and 34 healthy controls matched for age, gender and socio-demographic variables.

The children in the ALL survivor group were recruited from Pediatric Oncology Department, National Cancer Institute, Cairo University; evaluated and assessed in collaboration with the Psychiatry Department, Faculty of Medicine, Cairo University during the period of 6 months started in January, 2019.

ALL survivors initially diagnosed between 2008 and 2013, completed their treatment according to total XV protocol and were under follow up at least for 2 years.

Patients included in the study if they are confirmed acute lymphoblastic leukemia patients who ended treatment according to T XV protocol [6].

Age: 6 - 12 years old at study entry ≥ 2 years off treatment in continuous first remission (1st CCR), written informed consent from the parents or caregiver, any risk group.

Patients were excluded in case of relapse; patients received cranial or cranio-spinal irradiation, patients who underwent Bone Marrow transplantation, patients having Down syndrome or any other syndrome causing mental disability or showing psychiatric symptoms on CBCL [7].

Data of eligible patients were collected from medical records as sociodemographic data as age, sex..., etc., data at presentation including clinical picture,

signs and symptoms, WBC count, CSF cytology, brain imaging studies and other organ function tests. Protocol and chemotherapy agent received according to total XV protocol, response to therapy.

Semi structured interview with every study patients' caregiver was sustained to assess: developmental history whereas the caregiver is interviewed about the developmental milestones, any co-morbidities or chronic illness or psychiatric disorder, previous history of school performance.

Cognitive assessment was tested using the Wechsler Intelligence Scale for Children (WISC) (for age range 6 - 12 years) [8]. The WISC is a collection of 13 distinct subtests divided into two scales—a Verbal Scale and a Performance Scale. The six Verbal Scale tests use language-based items, whereas the seven Performance Scales use visual-motor items that are less dependent on language. The test was administrated by a clinical psychologist from Cairo University. The duration of the test range between 45 - 50 min per each case. Once a child's performance on a subtest is compared to the normative sample, subtest scores were converted into scaled scores that serve as one of the universal metrics for this test.

Child Behavior Checklist (CBCL) developed by Achenbach 6 for completion by parents. The scale consists of 113 questions to which the parents had to circle the 2 if the item is very true or often true of their child's behavior now or within the past six months; to circle the 1 if the item is somewhat or sometimes true and to circle the 0 if it is not true of their child. The total score could be obtained by summation of the scores of each statement, so it ranged between 0 and 224. The CBCL also contains different subscales showing the type of the problem namely: depressed, somatic complaints, social withdrawal, delinquent, aggressive and hyperactive.

All the human experiments were conducted with ethical standard and after written consent from the caregivers.

3. Results

61 children long-term survivors of childhood ALL and 34 healthy controls, 65.6% were males (**Table 1**). WISC III total scores showed significant difference between ALL survivors group and control group, control group showed higher values than ALL survivor group 98.7 ± 10.3 vs. 84.8 ± 10.0 respectively with p-value < 0.001.

Results showed significant difference in both verbal and performance IQ results between both groups, control group showed higher values than ALL survivors group with significant p-value < 0.001. This indicates that there is significant difference between the two groups regarding the cognitive functions (**Table 2**). When the two groups were compared to the normal ranges of the IQ there was significant difference as regard the total IQ scores with p-value < 0.001 in front of control group (**Figure 1**).

There was significant difference between the two groups in the subscales of

Table 1. Socio-demographic characteristics and treatment variables in survivors and control.

	ALL survivors	%	control	%
Number	61	64.2	34	35.8
Gender				
Males	40	65.6	21	61.8
Females	21	34.4	13	38.2
Residency				
Rural	27	44.3	12	35.3
Urban	34	55.7	22	64.7
Education				
In school	56	91.8	34	100
Not in school	5	8.1	0	0
Mean age	10		9	
Risk stratification				
Low risk	39	64	--	
Standard risk	22	36	--	

Table 2. WISC III results between ALL survivors and control group.

IQ	ALL Survivors N = 61 Mean ± SD	Control N = 34 Mean ± SD	P-value
Total	84.8 ± 10.0	98.7 ± 10.3	<0.001*
Verbal IQ	94.4 ± 13.5	110.1 ± 13.6	<0.001*
Information	8.1 ± 2.5	11.3 ± 2.8	<0.001*
Comprehensive	7.4 ± 2.8	9.1 ± 2.7	<0.006*
Arithmetic	8.3 ± 2.7	10.0 ± 3.0	<0.008*
Similarities	9.0 ± 3.0	10.3 ± 3.4	<0.048*
Vocabulary	7.6 ± 7.6	10.6 ± 2.3	<0.001*
Digit repetition	7.0 ± 1.8	8.8 ± 2.0	<0.001*
Performance IQ	76.6 ± 10.0	85.3 ± 8.5	<0.001*
Picture complete	6.4 ± 2.3	7.4 ± 2.0	<0.041*
Picture arrangement	6.6 ± 2.7	7.3 ± 1.3	<0.191
Blocks digits	7.5 ± 1.7	8.7 ± 2.0	<0.004*
Objects assembly	5.0 ± 1.8	6.8 ± 2.3	<0.001*
Coding	7.0 ±2.7	9.1 ± 2.0	<0.001*

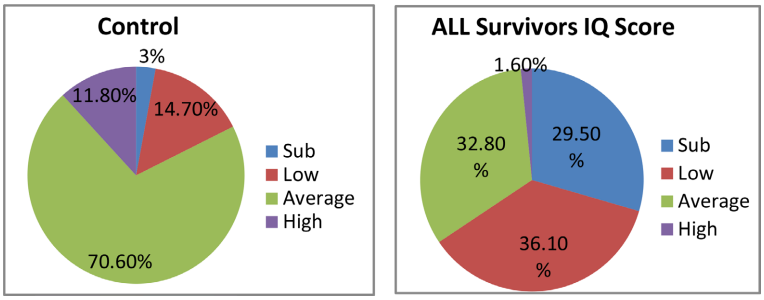

Figure 1. Percentage of results of IQ in each group.

Table 3. Relation between IQ Results and Gender

WISC III Scores	Males N = 40 Mean ± SD	Females N = 21 Mean ± SD	P-value
Verbal IQ	96.6 ± 14.3	90.1 ± 10.9	0.045*
Performance IQ	77.2 ± 10.8	75.4 ± 8.4	0.681
Total IQ	86.5 ± 10.2	81.5 ± 9.1	0.083*

the Verbal IQ with significant p-value. It indicated that the control group had better memory, social knowledge, logic thinking and attention (Table 2).

There was significant difference between the two groups in the subscales of the Performance IQ except for the picture arrangement subscale with significant p-value. It indicated that the control group had better perception, language, coordination and concentration (Table 2).

The study patients were followed up from 2 to 7 years with mean duration of 5 years. The number of survivors who completed three years follow up were 29 (47.5%) compared to 32 (52.4%) who were more than three years follow up. There was no significant difference in the cognitive affection between the two groups as regard Total, Verbal and Performance IQ.

There was significant difference between the two subsets regarding the Verbal IQ with p-value 0.045 with higher verbal IQ among males. The total WISC III score showed slight difference between males and females with insignificant p-value 0.083 (Table 3).

This showed that male survivors have better cognitive functions regarding memory, attention, logic thinking and social knowledge. There was no significant difference between the two subsets regarding the Performance IQ (p-value 0.681) with no difference in language, perception, co-ordination and concentration.

The study included 39 patient 64% with low risk disease and 22 patient 36% with standard risk disease, there was no significant difference between the two groups regarding cognitive affection despite the difference in intensity of chemotherapy received.

4. Discussion

The present study indicated that children treated for ALL early in life by

che-motherapy only showed decreased global neuro-cognitive functioning. Their achievements on Total IQ, Verbal IQ and Performance IQ, were all below the matched control group with (84.8 ± 10 vs. 98.7 ± 10.3), (94.4 ± 13.5 vs. 110.1 ± 13.6) and (76.6 ± 10 vs. 85.5 ± 8.5) respectively with statistically significant difference (p-value 0.001). Group comparisons of the profiles from the WISC-III subtests scores indicated decreased level in verbal functioning, complex problem solving for arithmetic tasks, attention and memory.

This agreed with results of Lofstad that stated group differences of specific cognitive functions was most striking and consistent for verbal function (Verbal IQ) and attention (Freedom from Distractibility Index) [2].

Data from Lofstad study indicated deficits in complex visual spatial problem solving as measured by Block Design (9.6 ± 3.0 vs. 11.7 ± 2.4) with p value 0.002 and Object Assembly (9.7 ± 3.9 vs. 11.3 ± 2.1) with p value 0.028, but not in the less abstract Picture Completion (9.9 ± 3.1 vs. 9.6 ± 2.8) with p value 0.747 and Picture Assembly (10.3 ± 3.2 vs. 11.5 ± 2.9) with p value 0.119 subtests, which load highly for detail recognition.

The ALL survivors in this study did not differ significantly from controls for long memory of learned facts, recognition and field-dependent visual tasks [2].

Khalifa *et al.* also found that the most pronounced effects on cognitive functions were observed in the survivors group who showed significantly lower verbal, performance and total IQ compared to controls [9]. They also stated that Survivors treated with modified CCG protocol showed a significant decrease in all cognitive tests compared to control ($p < 0.05$) [9].

As reported by khalifa *et al.* [9] comparison of different patient subgroups regarding verbal IQ (VIQ), performance IQ (PIQ) and total IQ (TIQ) was not significant except for survivor group who showed significant reduction of the VIQ ($p < 0.01$).

Survival patients showed significant reduction in arithmetic ability as well as in similarity subsets ($p < 0.01$). Specific decreases in verbal functions have been documented previously by Kingma *et al.* [10] The ALL survivors in their study performed significantly below a large Dutch normative group on Verbal IQ, but no other scores showed significant differences.

Among several studies reported over the last decade [4] [11] [12] a lower group mean total IQ in ALL survivors of 8.3 to 22.2 IQ points compared to a matched healthy controls in contrast to Kaemingk [13] who reported no major cognitive impairment in ALL survivors using chemotherapy only.

Documentation of delayed brain changes, most commonly in reduction in the white matter volume, calcification, changes in glucose utilization and abnormalities in event related potential (ERP), strengthen the hypothesis of decreased levels in cognitive functioning [2].

The present study showed slight significant difference between males and fe-males regarding total IQ scores (86.5 ± 10.2 vs. 81.5 ± 9.1) with p-value 0.083 and the Verbal IQ scores (96.6 ± 14.3 vs. 90.1 ± 10.9) with p-value 0.045. Males showed better cognitive functions compared to females in the ALL survivors'

group.

These results are in agreement with Sherief [14] that sex plays an important risk factor for deterioration of neuro-cognitive function in survivors of ALL treated with chemotherapy alone as there is significant differences in both verbal and performance IQ scores between girls and boys, with girls do worse than boys in all IQ parameters except in vocabulary and picture arrangement subtests.

This was stated in review of literature that several studies found differences in performance between girls and boys, with girls consequently performing more poorly than boys. There is no definite explanation for this disparity. It has been hypothesized that gender differences in brain maturation may underlie varying vulnerabilities between girls and boys. Increase in white matter during childhood has been demonstrated to be smaller in girls than in boys, which could make girls more vulnerable to neurotoxic effects of chemotherapy [15].

Jacola [16] also reported that females may be at increased vulnerability because of sex-based differences in white matter development, including greater increase and later peak volume in healthy males.

In another study it was found that females continued to be at greater risk for impulsivity and hyperactivity. These findings are consistent with existing research that identifies female sex as a risk factor; however, in the study they did not identify an appreciable impact of sex on neuro-cognitive ability at the end of therapy [17].

In our study the effect of intensified chemotherapy and age at diagnosis were studied in relation to their effect on cognition function, it showed no significant effects within the study ALL children.

However, in Jacola study their results suggest that treatment with higher-intensity CNS directed chemotherapy and younger age at diagnosis continue to confer increased risk for neurocognitive difficulties 2 years after therapy [16].

Also Sherief *et al.* [14] stated that young age of onset of chemotherapy appears to be more risky for developing cognitive dysfunction as there is significant difference in comparison patients whose age of onset of the disease below than those above 5 years old in Wechsler performance IQ scores (except in picture completion & mazes, there is no significant difference), at the same time there is no significant difference in Wechsler verbal IQ scores. In consistence with literature, young age at diagnosis was demonstrated to be a risk factor for cognitive dysfunction in children with ALL treated with chemotherapy only in a substantial number of studies.

It has by now been widely accepted that children younger than 5 years of age at diagnosis of ALL are more susceptible to long-term sequelae of treatment. It is becoming apparent that this applies not only to cranial irradiation, but also to CNS-directed chemotherapy [18].

In our study the effect of duration of follow up from end of treatment was studied on the cognition functions in ALL survivors, we studied after two years follow up and three years follow up after end of treatment with 29 survivors who

completed three years follow up compared to 32 who were more than three years follow up.

It showed no significant relation to affection of cognition function, increase or decrease of the duration does not affect the degree of cognition affection with p-value for total IQ scores 0.750.

It might be more reasonable to follow those patients for longer periods of time aiming at eliciting any potential difference with time.

This agrees with khalifa *et al.* [9] which stated that there was no significant correlation between chemotherapy duration and VIQ, PIQ, and TIQ in all groups (group IV survivors for two years or more).

On contrary Campbell reported that length of time since treatment was not found to consistently moderate the significant effects and therefore the extent to which it influences the findings remains unclear [19].

Krull also reported the increased risk for executive function impairments with increased time since diagnosis [20].

This pattern may result from several processes. First, executive functions develop throughout adolescence and well into adulthood, and early injury may alter the trajectory of development such that skills lag farther behind with passing years. In addition, survivors are at increasing risk for chronic health conditions as they age, and health conditions can have an impact on executive function. In this regard, time since diagnosis was also associated with increased risk for self-reported behavioral problems.

5. Conclusion

The present data strongly supports the hypothesis that early childhood ALL treated by chemotherapy only influences subsequent brain development and is followed by cognitive sequels as evidenced by Alias *et al.* [21], Liu *et al.* [22], Zając-Spychała *et al.* [23]. Females are more likely to have neuro-cognitive affection among survivors of childhood ALL treated with chemotherapy-only protocols. Age at diagnosis and risk stratification did not show significant differences between different groups. Therefore, further reduction of neurotoxic medications and less chemotherapy administration to ALL patients has to be always attempted in further protocols keeping the same or better survival rates.

Acknowledgements

Thanks to the patients and their family for contribution in the questionnaire. Thanks to the supervising professors for making this work sees the light.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Gustafsson, G., Schmiegelow, K., *et al.* (2000) Improving Outcome through Two

Decades in Childhood ALL in the Nordic Countries: The Impact of High-Dose Methotrexate in the Reduction of CNS Irradiation. *Leukemia*, **14**, 2267-2275. https://doi.org/10.1038/sj.leu.2401961

[2] Lofstad, G.E., Reinfjell, T., Hestad, K. and Diseth, T.H. (2009) Cognitive Outcome in Children and Adolescents Treated for Acute Lymphoblastic Leukaemia with Chemotherapy Only. *Acta Paediatrica*, **98**, 180-186. https://doi.org/10.1111/j.1651-2227.2008.01055.x

[3] Kanellopoulos, A. andersson, S., Zeller, B., *et al.* (2016) Neurocognitive Outcome in Very Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia after Treatment with Chemotherapy Only. *Pediatric Blood & Cancer*, **63**, 133-138. https://doi.org/10.1002/pbc.25690

[4] Hill, D.E., Ciesielski, K.T., Sethre-Hofstad, L., Duncan, M.H. and Lorenzi, M. (1997) Visual and Verbal Short-Term Memory Deficits in Childhood Leukemia Survivors after Intrathecal Chemotherapy. *Journal of Pediatric Psychology*, **22**, 861-870. http://www.ncbi.nlm.nih.gov/pubmed/9494322

[5] IBM® Corp., Armonk, NY, USA SPSS Statistics Version 22.

[6] Carroll, W.L., Bhojwani, D., Min, D.-J., *et al.* (n.d.) Pediatric Acute Lymphoblastic Leukemia I. New Approaches To Risk-Adapted Therapy For Childhood Acute Lymphoblastic Leukemia. http://ashpublications.org/hematology/article-pdf/2003/1/102/1713862/102_131a.pdf

[7] Achenbach, T.M. (1991) Manual for the Child Behavior Checklist/4-18 and 1991 Profile. University of Vermont, Burlington.

[8] Wechsler, D. (2002) The Wechsler Preschool and Primary Scale of Intelligence. Third Edition, the Psychological Corporation, San Antonio. https://doi.org/10.1037/t15177-000

[9] Khalifa, A.S., Bishry, Z., Tantawy, A.A.G., *et al.* (2014) Psychiatric Morbidity in Egyptian Children with Acute Lymphoblastic Leukemia and Their Care Providers. *Hematology/Oncology and Stem Cell Therapy*, **7**, 76-84. https://doi.org/10.1016/j.hemonc.2014.01.002

[10] Kaemingk, K.L., Carey, M.E., Moore, I.M., Herzer, M. and Hutter, J.J. (2004) Math Weaknesses in Survivors of Acute Lymphoblastic Leukemia Compared to Healthy Children. *Child Neuropsychology*, **10**, 14-23. https://doi.org/10.1076/chin.10.1.14.26240

[11] El Alfy, M., Ragab, I., Azab, I., Amin, S. and Abdel-Maguid, M. (2014) Neurocognitive Outcome and White Matter Anisotropy in Childhood Acute Lymphoblastic Leukemia Survivors Treated with Different Protocols. *Pediatric Hematology and Oncology*, **31**, 194-204. https://doi.org/10.3109/08880018.2013.871763

[12] Raymond-Speden, E., Tripp, G., Lawrence, B. and Holdaway, D. (2000) Intellectual, Neuropsychological, and Academic Functioning in Long-Term Survivors of Leukemia. *Journal of Pediatric Psychology*, **25**, 59-68. http://www.ncbi.nlm.nih.gov/pubmed/10820944

[13] Kingma, A., Van Dommelen, R.I., Mooyaart, E.L., Wilmink, J.T., Deelman, B.G. and Kamps, W.A. (2002) No Major Cognitive Impairment in Young Children with Acute Lymphoblastic Leukemia Using Chemotherapy Only: A Prospective Longitudinal Study. *Journal of Pediatric Hematology/Oncology*, **24**, 106-114. http://www.ncbi.nlm.nih.gov/pubmed/11990695

[14] Sherief, L.M., Sanad, R., ElHaddad, A., Shebl, A., Abdelkhalek, E.R., Elsafy, E.R., Attia, E.I., *et al.* (2018) A Cross-Sectional Study of Two Chemotherapy Protocols on

Long Term Neurocognitive Functions in Egyptian Children Surviving Acute Lymphoblastic Leukemia. *Current Pediatric Reviews*, **14**, 253-260. https://doi.org/10.2174/1573396314666181031134919

[15] Schatz, J., Kramer, J.H., Ablin, A. and Matthay, K.K. (2000) Processing Speed, Working Memory, and IQ: A Developmental Model of Cognitive Deficits Following Cranial Radiation Therapy. *Neuropsychology*, **14**, 189-200. http://www.ncbi.nlm.nih.gov/pubmed/10791859

[16] Jacola, L.M., Krull, K.R., Pui, C.H., *et al.* (2016) Longitudinal Assessment of Neurocognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia Treated on a Contemporary Chemotherapy Protocol. *Journal of Clinical Oncology*, **34**, 1239-1247. https://doi.org/10.1200/JCO.2015.64.3205

[17] Precourt, S., Robaey, P., Lamothe, I., Lassonde, M., Sauerwein, H.C. and Moghrabi, A. (2002) Verbal Cognitive Functioning and Learning in Girls Treated for Acute Lymphoblastic Leukemia by Chemotherapy with or without Cranial Irradiation. *Developmental Neuropsychology*, **21**, 173-195. https://doi.org/10.1207/S15326942DN2102_4

[18] Buizer, A.I., de Sonneville, L.M.J. and Veerman, A.J.P. (2009) Effects of Chemotherapy on Neurocognitive Function in Children with Acute Lymphoblastic Leukemia: A Critical Review of the Literature. *Pediatric Blood & Cancer*, **52**, 447-454. https://doi.org/10.1002/pbc.21869

[19] Campbell, L.K., Scaduto, M., Sharp, W., *et al.* (2007) A Meta-Analysis of the Neurocognitive Sequelae of Treatment for Childhood Acute Lymphocytic Leukemia. *Pediatric Blood & Cancer*, **49**, 65-73. https://doi.org/10.1002/pbc.20860

[20] Krull, K.R., Brinkman, T.M., Li, C., *et al.* (2013) Neurocognitive Outcomes Decades after Treatment for Childhood Acute Lymphoblastic Leukemia: A Report from the St. Jude Lifetime Cohort Study. *Journal of Clinical Oncology*, **31**, 4407-4415. https://doi.org/10.1200/JCO.2012.48.2315

[21] Alias, H., Lau, S.C.D., Schuitema, I. and de Sonneville, L.M.J. (2018) Neuropsychological Consequences for Survivors of Childhood Brain Tumor in Malaysia. *Frontiers in Psychology*, **9**, Article No. 703. https://doi.org/10.3389/fpsyg.2018.00703

[22] Liu, W., Cheung, Y.T., Conklin, H.M., Jacola, L.M., Srivastava, D., Nolan, V.G., Zhang, H., Gurney, J.G., Huang, I.C., Robison, L.L. and Pui, C.H. (2018) Evolution of Neurocognitive Function in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia Treated with Chemotherapy Only. *Journal of Cancer Survivorship*, **12**, 398-406. https://doi.org/10.1007/s11764-018-0679-7

[23] Zając-Spychała, O., Pawlak, M.A., Karmelita-Katulska, K., Pilarczyk, J., *et al.* (2020) Long-Term Brain Status and Cognitive Impairment in Children Treated for High-Risk Acute Lymphoblastic Leukemia with and without Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Center Study. *Pediatric Blood & Cancer*, **67**, e28224. https://doi.org/10.1002/pbc.28224

Appendix 1—List of Abbreviations

Abbreviation	Stands For
ALL	Acute Lymphoblastic Leukemia;
AML	Acute Myeloid Leukemia;
aPTT	Activated Partial Thromboplastin Time;
BASC	Behavior Assessment System for Children;
BRT	Brain radiation treatment;
BT	Brain tumors;
CBCL	Child behavior check list;
CDI	Children Depression Inventory;
CNS	Central Nervous System;
COG	Children Oncology Group;
CR	Complete remission;
CRT	Cranial Radiation Therapy;
CSF	Cerebrospinal fluid;
CT	Computed Tomography;
CU	Cairo University;
EEG	Electroencephalography;
EF	Executive functioning;
EFS	Event-free survival;
ETP	Early T-precursor;
FAB	French-American-British;
fMRI	Functional Magnetic Resonance Imaging;
GWAS	Genome-wide Association Studies;
HR	High risk;
ICD	International Classification of Disease;
IDDM	Insulin-dependent diabetes mellitus;
IQ	Intelligence Quotient;
IRB	Institutional review board;
LR	Low risk;
MEG	Magnetoencephalography;
MLL	Mixed-Lineage Leukemia;
MRD	Minimal residual disease;
NCI	National Cancer Institute;
NOS	Not Otherwise Specified;
PCR	Polymerase chain reaction;
PIQ	Performance IQ;
PT	Prothrombin Time;
PTSD	Post-traumatic stress disorder;
QOL	Quality of life;
RCMAS	Revised Children's Manifest Anxiety Scale;
RPM	Raven's Progressive Matrices;
SAI	School Ability Index;

SCD	Sickle cell disease;
SCT	Stem cell transplantation;
SDQ	Strengths and Difficulties Questionnaire;
SJCRH	St Jude Children's Research Hospital;
SR	Standard risk;
TIQ	Total IQ;
TLP	Traumatic lumbar puncture;
TPMT	Thiopurine methyltransferase;
VIQ	Verbal IQ;
WBC	White blood cells;
WHO	World Health Organization;
WISC	Wechsler Intelligence Scale for Children.