Neurocognitive Consequences of Childhood Leukemia and Its Treatment

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Abstract As survival rates have improved in pediatric patients with leukemia, late side effects from chemotherapeutics and radiotherapy have become important considerations. We investigated these side effects and evaluated their impact on neurocognitive functions. The observational study included 68 patients with acute leukemia who were treated at Eskişehir Osmangazi University Medical Faculty. The study also included 62 of the patients' closest age siblings as a control group. Demographic and clinical data, chemotherapy protocol, use of radiotherapy were recorded, neurological and ophthalmological examinations, cranial imaging, electroencephalography, visual evoked potential, and hearing investigations were performed, and neurocognitive functions were evaluated. At least one or more late effects detected by a neurologic abnormality on physical exam, cranial magnetic resonance imaging, neurological tests, or neurocognitive tests was significantly more likely in the patient group (82.4%) compared to the control group (29%, $p < 0.001$). A higher rate (82.4%) of delayed neurological and cognitive problems occurred in children who received radiotherapy, intrathecal and/or

systemic chemotherapy during leukemia treatment compared to age-matched siblings. Patients being treated for leukemia should be periodically evaluated for treatment-related side effects. Prophylactic interventions such cognitive training and maintenance of academic growth may offer the best hope of preventing late effects.

Keywords Cancer · Children · Leukemia · Neurocognitive functions

Introduction

The survival rate in leukemia has increased due to methods developed in the last 30 years for treatment of the disease as well as therapies to protect the central nervous system and advances in supportive care [1, 2]. As the survival rate and time have increased, early and late side effects arising from chemotherapeutics and radiotherapy used to treat leukemia have become important considerations [3, 4].

Side effects related to cancer treatment that occur after it is completed are defined as “late effects.” Late effects occur in two-thirds of pediatric cases [5], making long-term follow-up of patients treated for leukemia necessary [6]. Late effects have been reported to include growth and developmental retardation; cardiac toxicity; endocrinological, gastrointestinal, renal, and respiratory problems; puberty disorders; infertility; osteopenia/osteoporosis and bone fractures; visual and hearing disorders; secondary neoplasms; sensory and motor neurological dysfunction; psychiatric disorders; and cognitive dysfunction, depending on the chemotherapeutic agents and radiotherapy used [5, 7, 8]. Subsequent issues may include decreased academic success, attention deficit, dysmnnesia, difficulty with reading and arithmetic, disruption in visual perception, and

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occupational and social problems [9]. In this study, we aimed to investigate the late side effects of chemotherapy and radiotherapy used to treat acute leukemia in childhood and the impact of these effects on neurocognitive functions.

Methods

The Study Group

This study included 68 children who were aged at the time of diagnosis between 1 and 17 years with acute leukemia who were treated with ALL BFM 90/95, AML BFM 93 and 98 protocols at Eskisehir Osmangazi University, Medical Faculty, Division of Hematology-Oncology. Inclusion criteria were completion of maintenance therapies, absence of relapse, and survival of at least 1 year after the end of treatment. Patients who received any treatment in another center, experienced relapse, underwent stem-cell transplantation, or had central nervous system involvement were excluded from the study. A total of 130 subjects were included in the study, including a control group of 62 siblings who were not treated for leukemia and closest in age to the patients.

In order to collect data, the survivors over 18 years or the legal guardians of younger survivors were called by phone and informed about the study. Those who agreed to participate in the study were called to the outpatient clinic and informed consent was obtained. Participants' demographic data were recorded along with patients' information regarding the time elapsed since the end of maintenance treatment, chemotherapy protocol administered, risk group, number of intrathecal therapies, and the use of radiotherapy. The study was approved by the Eskisehir Osmangazi University, Medical Faculty Ethics Committee.

Control Group

It can be difficult to ascertain the neurocognitive effects of therapy without pre- and post-treatment testing, but that sibling testing can be used as a surrogate of this. The nearest-aged siblings of the patients who were included in the healthy control group at the step of neurocognitive tests. Only neurocognitive tests were done to siblings group. In order to eliminate all of the environmental factors that can affect the neurocognitive tests, the healthy sibling who lives in the same family with similar circumstances and nearest in age was recruited for the control group. The WISC-R tests were performed to siblings 6–17 years of age and WAIS-R tests were performed to siblings ≥ 18 years of age.

Evaluation of Neurologic and Neurocognitive Late Effects

Neurologic and neuropsychological late effects were evaluated mainly by neurological and visual examinations, cranial imaging, electroencephalography (EEG), visual evoked potential (VEP), and a hearing test were performed for each participant. Cognitive functions of the participants were evaluated using a battery of standardized neuropsychological examinations (Table 1). All testing was conducted by the same consultant psychologist, trained and supervised. The testing was conducted in a quiet room with minimal visual or audible distractions. Periods of rest were provided during testing to minimize the effect of fatigue.

The Wechsler Intelligence Scale for Children-Revised (WISC-R)

The Wechsler Intelligence Scale for Children-Revised (WISC-R) test was used for participants aged between 6 and 17 years. The standardization of the WISC-R for Turkish children was conducted by Savaşır et al. [10]. The WISC-R tests include two main parts including verbal and nonverbal parts. There are 12 subtests including verbal and performance skills. The total score is a good indicator of the level of intelligence. It is the gold standard measurement for the level of academic success. Psychometrically, the general mean value of the test is 100, and its standard deviation is 15. In our study, verbal subtests including general information, similarities, arithmetic, vocabulary, and serial digits, and performance subtests including picture completion, picture arrangement, block design, object assembly, and digit symbol were used.

The Wechsler Adult Intelligence Scale-Revised (WAIS-R)

The WISC-R was applied to evaluate general intellectual function. WAIS-R was used for the subjects aged at 18 years and older. WAIS-R is mainly used to measure the level of intelligence in adults and for neuropsychological evaluation. [11, 12]. The WAIS-R includes two main parts including verbal and nonverbal parts. The test is composed of verbal subtests including general information, vocabulary, arithmetic, judgment, similarities, and serial digits, and performance subtests including object assembly, picture completion, picture arrangement, block design, and digit symbol-coding.

The Serial Digit Learning Test (SDLT)

This test is the most commonly used to measure attention, short-term memory, and learning abilities. It is based on

Table 1 Neurocognitive test battery

Test	Applicable ages	Functions evaluated
Ankara Developmental Screening Inventory (ADSI)	Between 0 and 6 years	Parallel to the Denver II Developmental Screening test Language development Intellectual skills Small and large muscle development Social development, ability of self-care
Stroop Color and Word Test (SCWT)	6 years and older	The ability to inhibit one of two competing stimuli and to maintain attention for one
Serial Digit Learning Test (SDLT)	6 years and older	Attention/short-term memory test
Wisconsin Card Sorting Test (WCST)	6 years and older	Skills of abstraction and conceptualization Complex systems related with the frontal lobe
Bender Visual Motor Gestalt Test (BG)	Between 6 and 10 years	Measure brain damage and neurological deficit
Wechsler Intelligence Scale for Children-Revised (WISC-R)	Between 6 and 17 years	Neurocognitive functions Gold standard measurement for the level of academic success
Wechsler Adult Intelligence Scale-Revised (WAIS-R)	18 years and older	Neuropsychological evaluation Measure the level of intelligence

verbal presentation of 9 digits by the operator (1 digit per second). The teste should learn and repeat these digits 1 s after the serial is completed in their given order. The key point here is use of a learning strategy by the teste to not forget the digits. Studies have shown that this test enables activation of the prefrontal areas and hippocampal areas in the brain [13, 14].

Stroop Color and Word Test (SCWT)

This test measures the selective attention and response inhibition. The basic principle of the test is to create interference between word reading and color naming. The original test was developed by Stroop [15, 16] and its reliability and validity for the Turkish population was demonstrated by Karakas et al. [16]. The Stroop TBAG (Turkish Scientific and Technical Research Council of Turkey) form was standardized for Turkish children by Kilic et al. [16]. The SCWT measures the ability to inhibit one of two competing stimuli and to maintain attention for one, namely if the individual can alter his or her current perceptual status in the face of changing wishes. This test evaluates the strength of inhibiting distractor stimuli and holding response to inappropriate stimuli. Stroop TBAG has five subtests that sequentially involve reading color words that are printed black (ST-TBAG-1), reading color words that denote different colors (ST-TBAG-2), naming color of colored circles (ST-TBAG-3), naming color of colored neutral words (ST-TBAG-4), and naming color of colored words, where color and meaning are incongruent for some of the words (ST-TBAG-5).

Wisconsin Card Sorting Test (WCST)

The Wisconsin Card Sorting test was used to measure executive functions including attention, forming categories, and altering categories. The original test was developed by Berg [17] and the standardization of the WCST to the Turkish culture was made by Karakas et al. [16]. This test was developed to evaluate the skills of abstraction and conceptualization. It is also useful in evaluating complex systems related with the frontal lobe including the abilities to maintain the setup one has created, to alter this setup if necessary, and to plan the goal-directed actions.

Bender Visual Motor Gestalt Test (BG)

This test efficiently measures visual-motor perception, visual-motor functions, and cognitive development. In addition, it is useful in measuring the ability of visual-motor integration, the ability to correct errors, reaction in the face of problems, the ability for planning, and organization and motivation in children. The B-G test is used in measuring brain damage and neurological deficit. The Bender Visual Motor Gestalt test (BG) can only be used for children in a certain age group (6–10 years and 11 months) [18].

Ankara Development Inventory Test (AGTE)

This is an inventory used to evaluate children aged between 0 and 6 years in terms of development. Through use of the

ADSI, language development, intellectual skills, small muscle development, large muscle development, social development, and ability of self-care are scored by examining each individually and referring to the caregiver's information in infants and children starting from 0 to 3 months up to 48–72 months. It gives results in parallel to the Denver II Developmental Screening test [19].

Treatment Protocols

ALL BFM-90 and 95 protocols; The ALL BFM-90 treatment protocol was administered between 1995 and 1996 and the ALL BFM-95 was administered, thereafter. In both ALL BFM-90 and 95 protocols, patients were assigned to a standard-risk group (SRG), medium risk group (MRG), or high-risk group (HRG). Both protocols consist of 4 phases: induction, consolidation, reinduction, and continuation. In ALL BFM-90, preventive cranial radiotherapy was indicated for T cell ALL, MRG, and HRG patients with a dose of 12 Gy. Therapeutic irradiation dose for patients with initial involvement of the central nervous system was 12 Gy for patients 1–2 years and 24 Gy for patients more than 2 years of age. In ALL BFM-95, preventive radiotherapy was only indicated for T-cell ALL and HRG and CNS directed therapy dose was reduced to 18 Gy from 24 Gy. Infants younger than 1 year were neither preventively nor therapeutically irradiated. The ALL patients in MRG and SRG were given 11 doses of intrathecal treatment with methotrexate, those who were in HRG were given seven doses of intrathecal treatment with methotrexate and six doses of triple intrathecal treatment with methotrexate, prednisolone, cytarabine during the whole treatment period. Those with CNS involvement and in SRG and MRG had four additional doses of intrathecal methotrexate while those with CNS involvement and in HRG had four additional doses of intrathecal methotrexate and two additional doses of triple intrathecal treatment. The duration of treatment was 24 months for all patients in ALL BFM-90, 36 months in male MRG patients, and 24 months for all patients in ALL BFM-95 [20, 21].

AML BFM 93 and 98 protocols; The AML BFM-93 treatment protocol was administered between 1996 and 1998 and the AML BFM-98 was administered thereafter [22]. In AML-BFM 93, preventive cranial radiotherapy was indicated for all patients older than 1 year of age. Intrathecal cytarabine was given five times to SRG patients and six times to HRG patients following age-dependent dosage regimens. The dose was 15 Gy for patients 1–2 years and 18 Gy for patients more than 2 years of age. Therapeutic irradiation dose for patients with initial involvement of the central nervous system was 18 Gy for patients 1 to 2 years and 24 Gy for patients more than 2 years of age [22]. In AML-BFM-98, the dose of

preventive radiotherapy was reduced to 12 Gy. Therapeutic irradiation dose for patients with initial involvement of the central nervous system was 18 Gy. Infants younger than 1 year were neither preventively nor therapeutically irradiated [23].

Statistical Analysis

The data were analyzed using SPSS for Windows 13.0. Chi square (χ^2) test or Fisher's exact test was used for comparing categorical data, and Student's *t* test was used for continuous data. Kruskal–Wallis variance analysis was used for comparison of multiple groups that were not compatible with parametric distribution, and Spearman's rank correlation analysis was used to determine the correlation between the variables. A *p* value of ≤ 0.05 was considered significant for all analyses.

Results

A total of 68 children who with acute leukemia were included in the study. 65 of 68 patients (95.5%) had at least one sibling, among them only 62 siblings accepted to participate in the study. Participants were divided into two groups, under and over 6 years of age, based on the utility of the tests. The demographic data and clinical properties of the groups are summarized in Table 2.

On neurological examination, pathology that did not cause serious dysfunction was found in 2 patients (inability to walk at your fingertips, loss of muscle power in his right arm slightly) (2.9%). One patient (1.4%) was found to have abnormal EEG results, but there was no history of seizure and the central nervous system appeared free of organic disorder. Minor pathological findings (signal alternation in 9 patients, empty sella in 5 patients) were observed in 14 patients (20.6%) on magnetic resonance imaging (MRI). No pathology was found in the VEP test or through ophthalmological examination in any patient. Hearing deficit was found in 5 patients (7.3%).

The AGTE test was used for children less than 6 years of age. (10 patients, 14 siblings under 6 years of age). No significant difference was found between the sibling and patient groups in terms of AGTE development tests including the areas of general development, language-cognitive development, fine motor development, gross motor development, social abilities, and self-care.

WISC-R was applied to 50 subjects (86.2%) in the patient group and 37 subjects in the control group who were aged between 6 and 17 years. WAIS-R was applied to 8 subjects (13.8%) in the patient group and 11 subjects (22.9%) in the control group aged 18 years and older. No statistically significant difference was found between the

Table 2 Demographic and clinical properties

Properties	Patient group (<i>n</i> = 68)	Siblings (<i>n</i> = 62)	<i>p</i> value
Sex, <i>n</i> (%)			0.86
Female	33 (48.5)	31 (50)	
Male	35 (51.5)	31 (50)	
Diagnosis, <i>n</i> (%)			
AML	7 (10.3)		
ALL	61 (89.7)		
Mean age at the time of assessment, years $\pm$ SD	10.9 $\pm$ 4.6 (4–20)	11.5 $\pm$ 5.9 (1–23)	0.48
Mean age at the time of diagnosis, years $\pm$ SD	5.3 $\pm$ 3.8 (1–17)		
Time passed after treatment was completed, years $\pm$ SD	3.8 $\pm$ 3 (1–12)		
Group by age			0.24
<6 years	10 (14.7)	14 (22.6)	
$\geq$ 6 years	58 (85.3)	48 (77.4)	
Risk Group, <i>n</i> (%)			
Standard	27 (39.7)		
Moderate	32 (47.1)		
High	9 (13.2)		
Patients who had received radiotherapy, <i>n</i> (%)			
<6 years	4 (40)		
$\geq$ 6 years	30 (51.7)		
Methotrexate dose, <i>n</i> (%)			
1 g/m ²	36 (52.9)		
2 g/m ²	19 (27.9)		
5 g/m ²	6 (8.8)		
Treatment Protocol, <i>n</i> (%)			
ALL BFM 90	11 (16.2)		
ALL BFM 95	50 (73.5)		
AML BFM 2003	7 (10.3)		

patient and control groups in terms of verbal, performance, and total intelligence scores (Table 3).

The Stroop test (parts 2, 3, and 5) was used to evaluate the functions of the frontal lobe. Late effects in the at least one sub-group of the Stroop test was found in 30 subjects (62.1%) in the patient group and 11 subjects (22.9%) in the control group ($p < 0.001$). The patient group showed

significantly lower performance compared to the control group in terms of total time and number of incorrect answers.

When the groups were examined by using the Wisconsin Card Sorting test which evaluates the complex systems and executive functions related with the frontal lobe, late effects in the at least one sub-group of this test was found in 30 subjects (51.7%) in the patient group and 10 subjects (20.8%) in the control group ($p = 0.001$). The number of categories correctly sorted in the Wisconsin Card Sorting test was lower in the patient group compared to the control group ($p = 0.001$). While the number of perseverative responses was significantly higher in the patient group ($p = 0.001$), the conceptual response percent was found to be lower ($p < 0.001$). The score for failure to maintain set was significantly higher in the patient group ($p = 0.04$).

When the groups were examined by use of the Serial Digit Learning test (SDLT), which is most commonly used for short-term memory, the mean score was significantly lower in the patient group compared to the control group ($p = 0.003$; Table 3).

The Bender Visual Motor Gestalt test (BG) can only be used for children in a certain age group (6 years to 10 years and 11 months), and it was applied for 33 patients and 19 siblings. Late effect was found in 6 subjects (18.1%) in the patient group, but no impairment was found in the control group. The error score in Bender Gestalt visual perception was found to be significantly higher in the patient group compared to the control group ($p < 0.001$; Table 3).

When the subjects were evaluated in terms of all late side effects, impairment in at least one of the items, including physical examination, cranial MRI, neurological tests, and neurocognitive tests, was found to occur significantly more in the patient group (82.4%; $n = 56$) compared to the control group (29%; $n = 18$; $p < 0.001$).

For evaluation of the effects of radiotherapy on neurocognitive functions, patients who received chemotherapy only ($n = 34$) and those who received both radiotherapy and chemotherapy ($n = 34$) were examined as separate groups. A statistically significant difference was found between the two groups in terms of the number of perseverative responses and the number perseverative errors in the Wisconsin Card Sorting test ($p = 0.027$, $p = 0.026$, respectively, Table 4). However, no statistically significant difference was found with the Stroop test, Wechsler Intelligence Scale, and Serial Digit Learning test. Since these tests as well as the Wisconsin Card Sorting test cannot be used for patients below the age of 6 years, 10 patients from both groups were excluded from the assessment.

In the correlation analysis of risk factors in the patient group, correlations with cognitive function tests were evaluated in terms of age, sex, risk group, methotrexate

Table 3 Comparison of neurocognitive test results between the groups

Tests	Patient group		Siblings		<i>p</i> value
	<i>n</i>	Median (25%–75%)	<i>n</i>	Median (25%–75%)	
Wechsler (WISC-R)s	50		37		
Intelligence Scale for Children					
Verbal IQ		97.5 (89–108)		103 (90–111)	0.29
Performance IQ		100.5 (89–113)		100 (92–112)	1.00
Total IQ		100 (88–114)		101 (93–116)	0.55
Wechsler (WAIS-R)	8		11		
Adult Intelligence Scale					
Verbal IQ		100 (92–107)		100 (92–100)	0.43
Performance IQ		96.5 (84–106)		100 (82–100)	0.90
Total IQ		99.5 (91–107)		100 (88–104)	0.61
Stroop Test	58		48		
Late effects in the at least one sub-group of the Stroop test, (n, %)		30 (62.1)		11 (22.9)	<0.001
Wisconsin card Sorting Test	58		48		
Number of categories correctly sorted		4 (2–6)		6 (4–6)	0.001
Number of perseverative responses		38 (17.5–56)		21.0 (10.2–32.2)	0.001
Conceptual response percent		0.45 (0.27–0.65)		0.65 (0.53–0.76)	<0.001
Score for failure to maintain set		1 (0–2)		0 (0–1)	0.040
Late effects in the at least one sub-group of the Wisconsin test, (n, %)		30 (51.7)		10 (20.8)	<0.001
Serial Digit Learning Test	58	14 (7.7–19)	41	19 (15–21)	0.003
Bender Visual Motor Gestalt Test					
Number of errors	33	5.0 (3.0–8.5)	19	1.0 (0–4)	<0.001

IQ intelligent quotient

Table 4 Comparison of neurocognitive test results according to radiation treatment

Tests	Group that did not received radiotherapy		Group that received radiotherapy		<i>p</i> value
	<i>n</i>	Median (25%–75%)	<i>n</i>	Median (25%–75%)	
Wisconsin Card Sorting Test	28 ^a		30 ^a		
Number of categories correctly sorted		5 (2–6)		3 (1.2–6)	0.06
Number of perseverative responses		28.5 (12.7–46.0)		43.0 (25–69)	0.027
Number of perseverative errors		26.0 (12–40.5)		37.0 (22.5–53.7)	0.026
Conceptual response percent		0.54 (0.34–0.77)		0.38 (0.26–0.64)	0.94
Score for failure to maintain set		1 (0–1.25)		1 (0–2)	0.54

^a Since Wisconsin Card Sorting test could not be performed in children less than 6 years of age, 4 patients in the radiotherapy group and 6 patients in the non-radiotherapy group were not included in the assessment

(MTX) dose, number of intrathecal therapies, and administration of radiotherapy in single-variable Spearman correlation analyses. A low positive correlation was found between MTX dose and the duration of part 5 in the Stroop test ($r = 0.307$, $p = 0.025$). In addition, a low negative correlation was found between the number of intrathecal therapies and the score of the Serial Digit Learning test ($r = -0.311$, $p = 0.017$). A significant negative correlation was found between the ages of the children and the Stroop test durations (Stroop test parts 2, 3, and 5)

($r = -0.473$, $p < 0.001$; $r = -0.614$, $p < 0.001$; $r = -0.595$, $p < 0.001$, respectively).

Discussion

Children treated for cancer are at risk for neurocognitive late effects that produce declines in IQ, academic skills, and career attainment. The use of intensive chemotherapy (e.g., methotrexate) and radiation therapy are thought to

cause damage to cortical and subcortical white matter, resulting in these late effects. Symptoms consistent with attention-deficit disorder and deficits in mental processing speed, working memory, executive functioning, and memory combine to leave survivors intellectually and academically disadvantaged.

Neurocognitive functions, including intellect, attention, memory, planning, judgment, learning abilities, executive functions, ability to cope with distractors, and ability to suppress undesired reactions; neurological and neuroradiological findings; and hearing and visual abilities were evaluated at least 1 year after the end of treatment in 68 patients with acute leukemia who completed their therapies without relapse. Children who received radiotherapy and intrathecal and systemic chemotherapy during cancer treatment were found to have impairments in neurological and cognitive functions in the late term compared to their age- and sex-matched siblings.

In our study, the neuropsychological test performances of patients were found to be lower compared to the control group. Other studies evaluating late effects after treatment found similar effects [24, 25]. The rate of late effects in at least one of the items, including physical examination, cranial MRI, neurological tests, and neurocognitive tests, was found to be significantly higher (82.4%) in the patient group compared to the control group. It has previously been reported that at least one late side effect is observed in 62.3–75.1% of patients after treatment for acute leukemia [7, 26, 27]. Similarly, this rate has been reported to be 80% in our country [28]. The higher rate found in our study may be due to the tests that we performed being more comprehensive and more sensitive than those in other studies.

Although methotrexate and craniospinal irradiation are generally associated with poor neurocognitive outcome, this is not true for all children. Currently we do not have the ability to reliably predict in advance which patients will develop significant cognitive impairment and which will not. The mechanisms by which neurocognitive changes occur are also not well-understood. Knowledge of both of these is crucial if the neurocognitive sequelae are to be reduced or prevented.

The risk factors related with neurocognitive late side effects include being female, being less than 6 years of age at the time of diagnosis, receiving cranial radiotherapy at an early age, and receiving high-dose and intensive treatment related to being in a high-risk group [29, 30]. Similar to these studies, a low positive correlation was found between the MTX dose and the duration of Stroop test, a low negative correlation was found between the number of intrathecal therapies and the score of the Serial Digit Learning test, and a very strong negative correlation was found between the age at the time of diagnosis and the Stroop test durations; these were defined as risk factors.

Chemotherapy and especially radiotherapy below the age of 6 years has been reported to cause a marked reduction in IQ [29, 31]. A reduction in intellectual functions was noted in a large portion of the individuals who received cranial radiotherapy, and this reduction was linked to lower academic success and a reduction in the general quality of life [32, 33]. Reduced intellectual performance generally occurs years after treatment and tends to be progressive. Being female and having received radiotherapy at a young age increase the risk further [29]. Because of these factors, cranial radiotherapy has been removed from new ALL protocols. However, intellectual problems may still be observed in approximately 20–30% of patients. This outcome has been attributed mostly to administration of high-dose systemic MTX or intrathecal MTX, cytosine-arabinozide, and corticosteroid [34]. Neurocognitive side effects are observed more commonly in individuals who received ALL treatment in infancy and who have central nervous system involvement [35]. In our study, no statistically significant difference was found between the patient and control groups in terms of verbal, performance, and total intelligence subcategories. Since we could not compare the IQ tests before and after leukemia treatment, it was not possible to determine if a reduction occurred in IQ tests for these patients compared to the baseline. Therefore, it was not possible to evaluate the effect of leukemia treatment on IQ in this cross-sectional study. However, the rate of impairment in the Wisconsin Card Sorting test being higher in the patients who received radiotherapy compared to those who did not showed that a greater impairment occurred in the executive functions, which are among the functions of the frontal lobe.

Preventing these late effects is a challenge for both the medical team and for psychologists and rehabilitation specialists. Advances in neurosurgery, chemotherapy, and radiotherapy techniques are helping to a great extent, but may not be totally successful at preventing these late effects. Prevention depends in part on being able to predict those at greatest risk. There are a number of well-known risk factors for poorer neurocognitive outcomes, including demographic, medical, and treatment variables. Other predictors include genetic polymorphisms, neuroimaging, and acute sequelae of therapy. Patients may have risk-adapted therapy that seeks to lessen their morbidity.

Conclusion

Survivors of childhood leukemia are at risk of developing neurologic and neuropsychological late effects as a result of exposure to chemotherapy and radiotherapy. Thus, early identification of patients at risk for cognitive decline is an essential first step in the design of such preventive

intervention trials. Prophylactic interventions such cognitive training and maintenance of academic growth may offer the best hope of preventing late effects.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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