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Original Article

Neurocognitive and Neuroanatomical Changes in Children with Acute Lymphoblastic Leukemia Treated with the Modified BFM-95 Protocol

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Abstract

Background: The use of cranial radiotherapy for central nervous system (CNS) prophylaxis in children with acute lymphoblastic leukemia (ALL) is debated owing to its effect on neurocognitive functioning, as only <30% of the patients present with low risk in India and majority of the patients with high risk have to be treated with cranial radiation therapy (CRT) to prevent relapse. Given the increasing number of ALL survivors in India, the effect of CRT on neurocognitive functioning in children with ALL needs to be studied. **Methods:** Children (n = 44) with ALL who received CRT, intrathecal methotrexate (IT-MTX), and high-dose methotrexate (HD-MTX) for CNS prophylaxis as part of the modified Berlin-Frankfurt-Munster 95 protocol were included. Neurocognitive assessments and magnetic resonance image were performed to assess neurocognitive functioning and neuroanatomical structures, respectively. Five assessments were performed during the induction, end of re-induction I and II, commencement of maintenance, and end of maintenance phases of the modified BFM-95 protocol. Neurocognitive data of children with ALL were compared with those of healthy children (n = 60) at the baseline and after the final assessment. **Results:** A significant deterioration was observed in the performance intelligence, visuospatial ability, processing speed, and verbal retention domains after the completion of CNS prophylaxis. Three children had white matter changes on magnetic resonance imaging and showed reduced functioning in performance intelligence quotient, working memory, visual immediate and delayed memory, processing speed, verbal retention, visuospatial ability, processing speed, attention, planning and fine motor skills, and verbal comprehension. Children with ALL had poorer neuropsychological functioning when compared with healthy children. **Conclusion:** CNS prophylactic therapy as part of the BFM-95 protocol had an adverse effect on the neuropsychological functioning of children with ALL, and the effect was more pronounced when CRT was added to the treatment.

Keywords: *Acute lymphoblastic leukemia, BFM-95 protocol, central nervous system prophylactic treatment, chemotherapy, childhood cancer, cranial irradiation, neuropsychological functioning*

Introduction

Leukemia is the most common childhood cancer in India, with a relative proportion of 25%–40% of all cancers.[1,2] Acute lymphoblastic leukemia (ALL) accounts for 65%–85% of all leukemia cases reported.[1,3] Cure rates of childhood ALL have improved from virtually 0 in the 1950s to 90% currently in Western countries.[4] Overall survival outcomes at tertiary cancer centers in India (Mumbai, Chennai, and Bangalore) range from 65% to 70%.[5] Central nervous system (CNS) prophylaxis is a vital part of ALL treatment as it decreases the risk of CNS relapse and is greatly responsible for the remarkable increase in survival rates.[5-9] Intrathecal methotrexate (IT-MTX), intravenous high-dose methotrexate (HD-MTX), cranial radiation therapy (CRT), triple IT chemotherapy, or a combination of these modalities is commonly used to treat ALL.[10,11] The use of CRT, HD-MTX, or IT-MTX is based on patient risk stratification. At present, HD-MTX is only administered to patients with T-cell ALL or high-risk patients with B-cell ALL, and CRT is reserved for patients with overt CNS disease.[11-13] In the past, most patients in India received CRT as the treatment was not risk stratified; however, most centers have now moved toward risk-adapted therapy.[5-9,14]

With the rate of ALL survivors increasing in India, the need to study the effects of ALL treatment protocol including CRT on neurocognitive functioning is increasing.

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The modified BFM-95 protocol is used at the Cancer Institute (Chennai) which includes a combination of intravenous MTX, IT-MTX, and CRT. No prospective studies on the effect of any of these protocols have been conducted in India. Therefore, this prospective study was conducted to evaluate the effect of the modified BFM-95 protocol on neurocognitive functioning in children with ALL.

Methods

The study was conducted between 2011 and 2015. Ethical clearance was obtained before the initiation of the study. Children aged 6–15 years, who received the diagnosis of ALL- and CNS-directed therapy including HD-MTX, IT-MTX, and CRT, were included in the study. Furthermore, the children had to be attending regular school for inclusion in the study. Children with a history of any neurological disorder, psychiatric disorder, severe head injuries, disease relapse, and secondary malignancy at the time of assessment were excluded from the study. The control group included healthy children from local communities who attended regular school and matched the patients with ALL in age, sex, and socioeconomic status. The details of the sample recruited are presented in Figure 1. Children with ALL were from different geographical locations of Tamil Nadu and Andhra Pradesh, and healthy children were from Chennai.

Procedures and tools used

Written informed consent was obtained from the parents of children aged <12 years. A total of five neuropsychological assessments were completed at different phases of the modified BFM-95 treatment protocol.

The details of the tools used in the study are summarized in Table 1. Briefly, for the battery of tests used to assess neurocognitive function, higher scores indicated better performance. Some tests considered processing time and evaluated the performance level. T2-weighted, axial three-dimensional, spoiled gradient, and high-resolution MR images were collected using a 1.5 T MRI scanner to examine the neuroanatomical structures.

The baseline assessment was completed immediately after the initiation of the induction phase when the patient's general health condition is stable. Most children

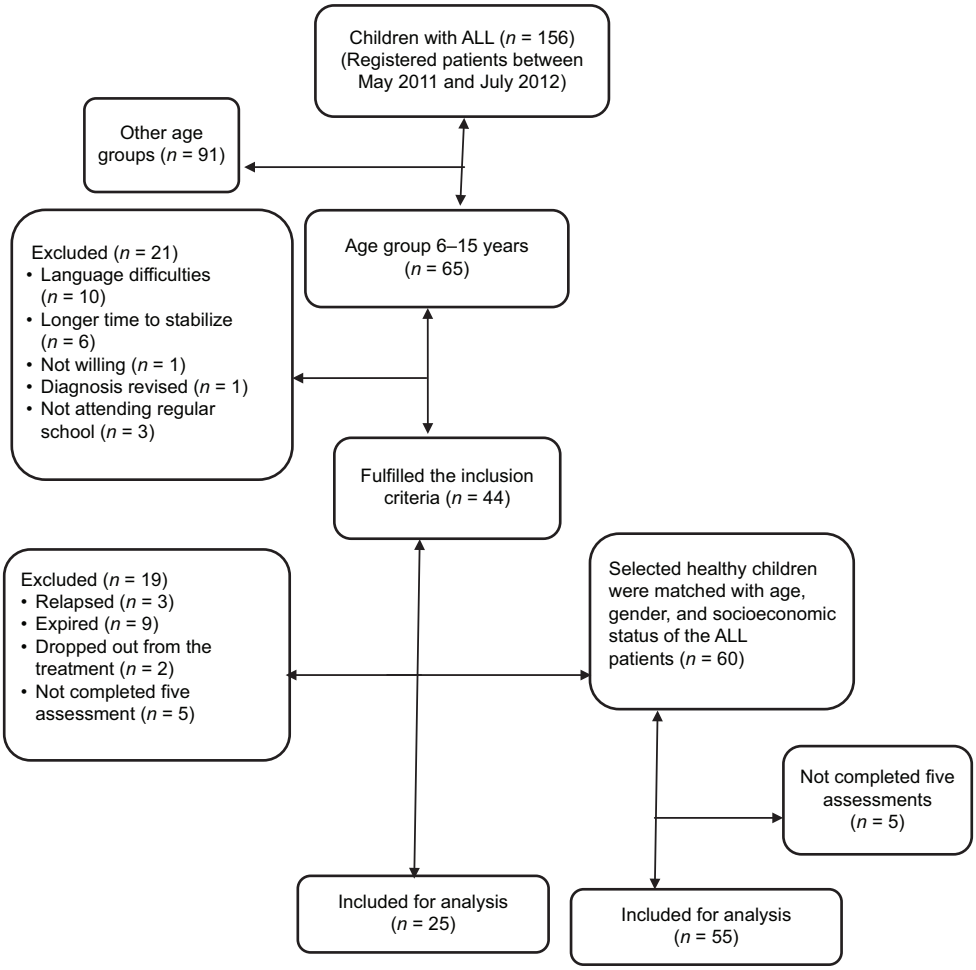

Figure 1: Flowchart of sample recruitment

Table 1: Neurocognitive test battery and MRI used and its outcome measures

Tools name	Author and year	Functions assessed
MISC - An Indian adaptation of the WISC	Malin (1969)[15]	PIQ
Sub tests of MISC		
Picture completion		Visuo-conceptual
Block design		Visuospatial
Coding		Processing speed
Object assembly		Perceptual organization
Maze		Planning and fine motor
The NIMHANS neuropsychological battery for children	Kar *et al*., (2004)[16]	
Sub tests of the NIMHANS battery		
Finger tapping test		Motor speed
Color cancellation test		Sustained attention
CT		Focused attention
Token test		Verbal comprehension
Verbal n-back test		Verbal working memory
Visuospatial span test		Visuospatial working memory
Auditory verbal learning test		Verbal learning and Memory
Memory for design test		Visual learning and Memory
MRI		Neuroanatomical structure

MISC – Malin's Intelligence Scale for Indian Children; MRI – Magnetic resonance image; WISC – Wechsler Intelligence Scale for Children; NIMHANS – National Institute of Mental Health and Neurosciences; PIQ – Performance intelligence quotient; CT – Color Trails Test

with ALL presented with poor general health; therefore, the first phase of chemotherapy, which included two or three doses of IT-MTX chemotherapy, was commenced immediately after diagnosis (on days 1, 7, and 15). The second and third assessments were conducted at the end of the re-induction I and re-induction II treatment phases, respectively. During the third assessment, the patients had completed CNS direct radiation therapy (1800 cGy). The fourth assessment was completed immediately after the commencement of the maintenance phase, which was 1 year from the time of diagnosis. The fifth assessment was completed at the end of the maintenance phase, which was 2 years from the time of diagnosis. The details of the assessment interval between the different phases of the modified BFM-95 protocol are presented in Figure 2. Routine treatment, investigations, and other medical procedures were not affected during the study period.

All the patients included in the study who presented for the fourth assessment (n = 25) underwent a contrast-enhanced MRI (brain) scan. Only eight children with ALL who were suspected to have neurotoxicity underwent MRI during the induction phase. MRI was not performed for other patients.

Baseline assessment for the healthy children was completed at the time of recruitment of the children with ALL, and postassessment was completed during the fifth assessment period of children with ALL, which was 2 years from the baseline assessment. The assessments were carried out by the researcher who has trained in neuropsychological assessments at the National Institute of Mental Health and Neuroscience, Bangalore. The total duration of the assessments was approximately 3–4 h. To overcome the effect of fatigue, the tests were administered in 1.5-h sessions with at least one 5–15 min break.

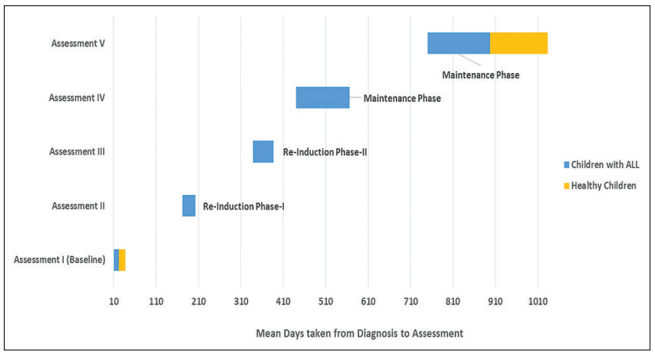

Figure 2: Assessment interval between the different phases of the modified BFM-95 protocol

Statistical analysis

Descriptive statistics were used to summarize demographic variables and clinical variables. Chi-square and independent sample t-tests were performed to find the difference in the demographic variables and neurocognitive functions between children with ALL and healthy children. General linear model one-way repeated measures analysis of variance (ANOVA) used to test for change over time (baseline, intensive phase treatments, and maintenance) in performance on the neurocognitive measures. Pairwise comparisons were calculated using the Bonferroni correction to evaluate whether differences in outcome scores at different measurements were significant. Statistical analyses were performed with the IBM Corporation. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. (Armonk, New York: IBM Corporation) with the alpha level set to 0.05 for all analyses.

Table 2: Demographic and clinical characteristics of children with acute lymphoblastic leukemia and demographic characteristics of healthy children

Variables	Children with ALL (*n*=25), *n* (%)	Healthy children (*n*=55), *n* (%)	t/χ^2	*P*
Age in years at the time of first assessment (baseline)				
Mean±SD	8.76±2.26	9.42±2.07	1.28*	0.20
Range	6-13	6-13		
Age in years at the time of final assessment (final)				
Mean±SD	10.76±2.26	11.42±2.07	1.25*	0.21
Range	8-15	8-15		
6-10 years	20 (80)	32 (58.2)		
11-15 years	5 (20)	23 (41.8)		
Gender				
Male	16 (64)	31 (56.4)	0.41	0.52
Female	9 (36)	24 (43.6)		
Education in years (baseline)				
Mean±SD	3.92±2.21	4.58±2.32	1.42*	0.16
Range	1-8	1-8		
Handedness				
Right hand	25	55		
Mother tongue				
Tamil	18 (72)	55		
Income (monthly income in Rupees) (INR)				
<5000	18 (72)	36 (65.5)	1.40	0.49
5000-10,000	5 (20)	17 (30.9)		
>10,000	2 (8)	2 (3.6)		
Family type				
Joint family	12 (48)	17 (30.9)	2.80	2.46
Nuclear family	13 (52)	38 (69.1)		
Consanguineous marriage				
Yes	13 (52)	6 (10.9)	16.02	0.00*
Literacy				
Father				
Schooling	16 (64)	41 (74.5)	3.79	0.15
Graduate	5 (20)	12 (21.8)		
Illiterate	4 (16)	2 (3.6)		
Mother				
Primary	17 (68)	49 (89.1)	5.29	0.07
Graduate	4 (16)	3 (5.5)		
Illiterate	4 (16)	3 (5.5)		
Occupation				
Father				
Unskilled	11 (44)	20 (36.4)	0.55	0.75
Semiskilled	6 (24)	13 (23.6)		
Skilled	8 (32)	22 (40)		
Mother				
Homemaker	17 (68)	29 (52.7)	5.91	0.11
Unskilled	5 (20)	20 (36.4)		
Semiskilled	3 (12)	2 (3.6)		
Skilled	-	4 (7.3)		
Risk stratification				
Low	1 (4)			
Intermediate	10 (40)			
High	14 (56)			
Immunophenotype				
T-cell	19 (76)			

Contd...

Table 2: Contd...

Variables	Children with ALL (*n*=25), *n* (%)	Healthy children (*n*=55), *n* (%)	t/χ^2	*P*
B-cell	6 (24)			
Neurotoxicity				
Seizure	2 (8)			
CVT	1 (4)			
Meningitis	1 (4)			
Headache	2 (8)			
No neurotoxicity	19 (76)			

*t-test. Significance level at 0.05. χ^2 – Chi-square test; ALL – Acute lymphoblastic leukemia; SD – Standard deviation; CVT – Cerebral venous thrombosis

Table 3: Mean, standard deviation, and *F* and *P* values of neurocognitive assessment scores of children with acute lymphoblastic leukemia

Neurocognitive functions	Mean±SD					*F*	*P*	η^2
	First assessment	Second assessment	Third assessment	Fourth assessment	Fifth assessment			
Overall PIQ	108.93±12.66	111.27±12.04	108.60±12.45	104.44±11.90	97.63±10.18	13.85	0.01**	0.74
Visuo-conceptual	111.00±21.13	110.24±17.68	108.68±17.68	108.04±12.48	103.40±16.34	1.58	0.84	0.15
Visuospatial	116.16±24.63	117.56±20.53	112.44±22.78	105.88±20.93	103.24±22.59	4.60	0.01**	0.37
Processing speed	111.24±21.72	113.32±20.31	112.68±18.57	107.40±16.61	92.92±15.12	10.61	0.01**	0.56
Perceptual organization	98.04±24.03	100.04±24.88	93.72±18.33	94.88±22.10	89.12±16.14	1.40	0.23	0.16
Planning and fine motor	110.00±10.41	115.36±17.93	110.72±19.61	109.76±18.55	105.80±20.07	1.32	0.26	0.19
Verbal retention	103.55±16.47	91.30±14.55	96.74±12.13	90.73±10.82	92.10±11.44	4.31	0.01**	0.30
Motor speed (RH)	32.22±5.62	34.45±6.17	35.13±5.74	37.24±5.66	40.10±8.79	23.59	0.01**	0.75
Motor speed (LH)	27.06±5.55	29.44±6.50	29.70±5.75	31.31±6.13	33.48±6.76	16.15	0.01**	0.72
Verbal learning	49.92±8.21	51.96±9.74	52.64±9.06	54.24±10.29	58.32±8.55	10.46	0.01**	0.58
Verbal immediate memory	10.76±2.52	10.80±2.54	11.28±2.03	11.48±2.20	11.64±1.97	1.41	0.23	0.18
Verbal delayed memory	11.44±2.27	10.84±2.46	11.60±2.25	11.92±2.08	12.00±2.36	1.86	1.22	0.26
Visual learning	69.20±11.78	69.72±11.98	70.16±12.08	72.48±10.82	74.24±7.49	4.26	0.01**	0.30
Visual immediate memory	9.84±3.21	10.56±2.73	10.80±2.91	10.68±2.49	11.24±3.12	2.66	0.03*	0.30
Visual delayed memory	9.76±3.16	9.88±3.05	10.28±2.82	10.52±2.38	11.72±3.00	9.07	0.01**	0.62
Sustained attention#	91.20±36.72	82.52±36.93	78.80±23.79	75.88±21.64	77.56±24.77	2.31	0.06	0.21
Focused attention (CT-A)#	121.96±71.70	101.84±56.39	92.88±51.79	85.52±48.60	79.32±32.81	7.30	0.01**	0.39
Focused attention (CT-B)#	240.08±137.42	212.64±130.36	193.12±72.96	160.24±51.66	160.68±71.88	6.52	0.01**	0.65
VW memory (NB 1)	8.28±0.97	8.20±1.00	8.04±1.05	8.16±0.74	8.16±1.34	0.27	0.89	0.05
VW memory (NB 2)	10.48±2.48	10.24±2.52	10.12±2.4	9.80±2.17	10.20±1.84	0.47	0.75	0.10
VSWM-F	4.24±0.83	4.08±0.99	4.08±1.07	4.52±0.50	4.64±0.70	3.78	0.01**	0.32
VSWM-B	2.56±1.66	2.48±1.71	2.32±1.54	2.42±1.55	2.56±1.50	0.28	0.88	0.05
Verbal comprehension	31.86±5.05	31.86±4.26	31.58±3.33	31.52±3.27	32.02±3.53	0.15	0.96	0.01

#Score indicates time in seconds (as lesser the time, better the performance); *P<0.05, **P<0.01. ALL – Acute lymphoblastic leukemia; SD – Standard deviation; PIQ – Performance intelligence quotient; RH – Right hand; LH – Left hand; CT-A – Color Trails Test A; CT-B – Color Trails Test B; NB 1 – N-back test 1; NB 2 – N-back test 2; VSWM-F – Visuospatial working memory-forward; VSWM-B – Visuospatial working memory-backward; SD – Standard deviation; VW – Verbal working memory

Results

Demographic and clinical characteristics of children with ALL and demographic characteristics of healthy children included in the study are summarized in Table 2. There was no significant difference based on age, sex, education, socioeconomic status, family type, and parents' literacy and occupation between children with ALL and healthy children. In the experimental group, 52% of the children born to parents from a consanguineous marriage, whereas it was 10.9% in the control group, and the difference was statistically significant. The mean age at the time of baseline assessment was 8.76 ± 2.26 years for children with ALL and 9.42 ± 2.07 years for healthy children. The mean age of children at the time of final assessment was 10.76 ± 2.26 years for children with ALL and 11.42 ± 2.07 years for healthy children. Of the children with ALL, 64% were male, and of the healthy children, 56.4% were male. Clinical evaluation showed that most children with ALL were presented with high risk (56%) or intermediate risk (40%). Most children (76%) had T-cell immunophenotype. Neurotoxicity was observed in 24% of the children with ALL.

Changes in neurocognitive performance scores of children with acute lymphoblastic leukemia

The results from the general linear model for repeated measures ANOVA and within-subjects contrast are shown in Table 3. There was a significant change in mean scores in overall performance intelligence quotient (PIQ), visuospatial ability, processing speed, verbal retention, learning (verbal and visual), memory (visual immediate and delay), motor speed (right and left hand), focused attention, and executive function (visuospatial working memory-forward) across the five assessments. Mean scores for overall PIQ, visuospatial ability, processing speed, and verbal retention decreased significantly after the third, fourth, and fifth assessments as compared to the scores after the first and second assessments. However, the mean scores for verbal retention, learning (verbal and visual), memory (visual immediate and delay), motor speed (right and left hand), focused attention, and executive function (visuospatial working memory-forward) increased from baseline to the subsequent assessments. No significant difference was observed in the neurocognitive functions such as visuo-conceptual ability, perceptual organization, planning and fine motor skills, immediate verbal memory, delayed verbal memory, sustained attention, verbal working memory (n-back 1 and 2), visuospatial working memory (backward), and verbal comprehension.

The results of Bonferroni pairwise comparison analyses are shown in Table 4. Overall PIQ, visuospatial ability, processing speed, and verbal retention decreased gradually overtime, whereas a significant difference was observed between the fourth and fifth assessments in comparison with the other assessments. However, motor speed, verbal learning, visual delayed memory, and focused attention were found to steadily increase over time. Significant differences were observed in motor speed across the assessments; differences in other domains were pronounced in the fourth and fifth assessments.

Comparison of neurocognitive function of children with acute lymphoblastic leukemia and healthy controls

The results were analyzed using the independent *t*-test and are summarized in Table 5. At baseline, the results revealed no significant difference between children with ALL and healthy children except for verbal immediate memory and visual delayed memory. At postassessment, the results showed a significant difference in PIQ, visuo-conceptual ability, visuospatial ability, processing speed, perceptual organization, planning and fine motor skills, verbal comprehension, verbal working memory, visuospatial working memory, verbal immediate memory, verbal delayed memory, and visual immediate memory; no significant difference was observed in motor speed (left and right hand), learning (verbal and visual), visual delayed memory, sustained attention, and focused attention (color trails test A). The results show that children with ALL had poorer scores than healthy children on most of the neurocognitive function at postassessment (fifth assessment).

Neuroanatomical changes in children with acute lymphoblastic leukemia

Neuroanatomical changes were assessed using the results of MRI. The sample details are summarized in Table 6. The baseline MRI of the eight children with ALL suspected to have neurotoxicity showed no abnormalities in the brain. Of these, two children experienced neurotoxicity during the intensive phase of treatment. Of the 25 children with ALL evaluated at the maintenance phase, abnormalities on MRI were observed for three children: white matter changes (best depicted in T2-weighted sequences) in periventricular deep white matter regions extending to the centrum semiovale were noted in two patients (Grade II) and in periventricular cortex in the left parietal region posteriorly (Grade I) in one patient. The MRI (brain) images of the children with ALL who had changes are shown in Figure 3.

Table 4: Pairwise comparisons between the five assessments on neurocognitive functions in children with acute lymphoblastic leukemia (*P* values)

Functions Neurocognitive functions	First versus second	First versus third	First versus fourth	First versus fifth	Second versus third	Second versus fourth	Second versus fifth	Third versus fourth	Third versus fifth	Fourth versus fifth
Overall PIQ				0.001		0.005	0.001		0.001	0.008
Visuospatial						0.041	0.031			
Processing speed				0.005			0.001		0.001	0.002
Verbal retention			0.051							
Motor speed (RH)	0.001	0.001	0.001	0.001		0.004	0.001		0.003	
Motor speed (LH)	0.001	0.047	0.001	0.001			0.004		0.009	
Verbal learning				0.001			0.002		0.011	
Visual delayed memory				0.001			0.002		0.014	
Focused attention (CT-A)[#]			0.023	0.011						
Focused attention (CT-B)[#]			0.023	0.012				0.009	0.002	

[#]Score indicates time in seconds (as time taken reduces performance increases). Significant level at 0.05. PIQ – Performance intelligence quotient; RH – Right hand; LH – Left hand; CT-A – Color Trails Test A; CT-B – Color trails test B

Table 5: Comparison of baseline and postassessment scores of children with acute lymphoblastic leukemia and healthy children

Neurocognitive functions	Baseline assessment				Postassessment			
	Mean±SD		*t*	*P*	Mean±SD		*t*	*P*
	Children with ALL	Healthy children			Children with ALL	Healthy children		
Overall PIQ	108.93±12.66	110.95±10.80	0.73	0.46	97.63±10.18	118.32±5.85	11.5	0.01*
Visuo-conceptual	111.00±21.32	113.80±15.47	0.66	0.50	103.40±16.34	123.40±10.15	6.69	0.01*
Visuospatial	116.16±24.63	115.50±19.69	0.12	0.90	103.24±22.59	116.21±6.92	3.90	0.01*
Processing speed	111.24±21.72	115.72±21.69	0.85	0.39	92.92±15.12	119.29±10.47	9.03	0.01*
Perceptual organization	98.04±24.03	100.76±18.95	0.52	0.59	89.12±16.14	111.67±8.98	8.01	0.01*
Planning and fine motor	110.00±10.41	112.34±12.04	0.84	0.40	105.80±20.07	120.00±12.08	3.92	0.01*
Verbal retention	103.55±16.47	102.63±8.58	0.33	0.74	92.10±11.44	98.61±4.94	3.36	0.01*
Motor speed (RH)	32.22±5.62	34.64±5.24	1.87	0.06	40.10±8.79	37.58±4.34	2.48	0.01*
Motor speed (LH)	27.06±5.55	28.87±5.54	1.35	0.18	33.48±6.76	33.74±6.00	0.17	0.86
Verbal learning	49.92±8.21	51.16±8.14	0.63	0.53	58.32±8.55	55.98±6.15	1.38	0.16
Verbal immediate memory	10.76±2.52	11.94±2.39	2.01	0.04*	11.64±1.97	13.20±1.26	4.25	0.01*
Verbal delayed memory	11.44±2.27	12.01±2.23	1.06	0.28	12.00±2.36	13.56±1.16	3.97	0.01*
Visual learning	69.20±11.78	70.27±13.80	0.33	0.73	74.24±7.49	76.52±12.74	0.83	0.40
Visual immediate memory	9.84±3.21	10.83±3.36	1.24	0.21	11.24±3.12	12.90±1.19	3.46	0.00**
Visual delayed memory	9.76±3.16	11.41±3.31	2.10	0.03*	11.72±3.00	12.56±0.87	1.92	0.10
Sustained attention[#]	91.20±36.72	82.34±36.37	1.00	0.31	77.56±24.77	69.58±24.02	1.36	0.17
Focused attention (CT-A)[#]	121.96±71.70	113.54±61.70	0.53	0.59	79.32±32.81	92.87±39.26	1.50	0.13
Focused attention (CT-B)[#]	240.08±137.42	235.70±120.12	0.14	0.88	160.68±71.88	131.29±39.19	2.36	0.02*
VW memory (NB 1)	8.28±0.97	8.47±0.74	0.97	0.33	8.16±1.34	8.83±0.37	3.47	0.01*
VW memory (NB 2)	10.48±2.48	11.36±1.82	1.78	0.07	10.20±1.84	12.85±1.40	7.07	0.01*
VSWM-F	4.24±0.83	4.29±0.80	0.25	0.79	4.64±0.70	3.52±1.10	4.62	0.01*
VSWM-B	2.56±1.66	2.69±1.69	0.32	0.74	2.56±1.50	3.52±1.10	3.23	0.01*
Verbal comprehension	31.86±5.05	33.15±4.38	1.15	0.25	32.02±3.53	35.34±0.798	6.66	0.01*

[#]Score indicates time in seconds (as time taken reduces performance increases); *$P<0.05$; **$P<0.01$. ALL – Acute lymphoblastic leukemia; SD – Standard deviation; PIQ – Performance intelligence quotient; RH – Right hand; LH – Left hand; CT-A – Color Trails Test A; CT-B – Color Trails Test B; NB 1 – N-back test 1; NB 2 – N-back test 2; VSWM-F – Visuospatial working memory-forward; VSWM-B – Visuospatial working memory-backward; VW – Verbal working memory

Table 6: Details of MRI (brain) with contrast of children with acute lymphoblastic leukemia

Variables	Baseline MRI	Post-MRI
Number of patients assessed, *n*	8	25
Male/female	4/4	16/9
Age (years), mean±SD	8.76±2.26	10.76±2.26
Time between diagnosis and MRI (days), mean±SD	76.20±49.63	502.79±63.36
Changes observed in MRI, *n* (%)	-	3 (12)

MRI – Magnetic resonance image; SD – Standard deviation

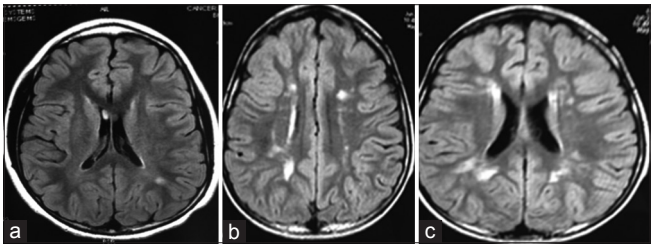

Figure 3: Images of T2-weighted MRI (brain) for three children with acute lymphoblastic leukemia who showed abnormalities. (a) Grade I: 13-year-old female. (b) Grade II: 8-year-old male. (c) Grade II: 6-year-old male

The white matter areas that were affected are associated with memory, executive functions, and processing speed. Analysis of postassessment data of the three patients revealed a reduced mean score for PIQ, working memory, visual immediate and delayed memory, processing speed, verbal retention, visuospatial ability, attention, planning and fine motor skills, and verbal comprehension, with further decrease in the fourth and fifth assessments as compared to the baseline.

Discussion

This study assessed the neurocognitive functioning of children with ALL treated with the BFM-95 protocol in comparison with that of healthy controls. The results showed that the combination of CRT and IT-MTX along with HD-MTX as part of the modified BFM-95 protocol (CNS prophylaxis) affected the neurocognitive functioning of children with ALL. Mild changes in neurocognitive functioning, following the intensive phase of chemotherapy, were observed (IT-, HD-MTX); however, a significant effect was observed with the addition of CRT. Children with ALL had poorer neurocognitive functioning when compared to healthy children. Children with ALL who had MRI abnormalities performed poorly on most of the neurocognitive tests.

Significant effects in four specific domains of neurocognitive functioning, namely PIQ, processing speed, visuospatial ability, and verbal retention functioning, were observed.

We also evaluated PIQ using the Malin's Intelligence Scale for Indian Children (MISIC) test. Across the five assessments, among children with ALL, PIQ significantly decreased at the fourth and fifth assessments, as compared to the first, second, and third assessments after receiving CNS prophylactic therapy along with HD-MTX.[17] Although a difference in the mean was noted, PIQ fell within the average range of 90–109 as per Wechsler IQ classification in all the five assessments for all the children except two children with ALL (80–89).[15] The mean score was the highest at the second assessment. This could be explained by the fact that the first assessment was performed immediately after the diagnosis and during the induction period, when the child was coping with the diagnosis, the new environment, and the treatment procedures. Both children with ALL and healthy children performed similarly at the baseline, whereas children with ALL performed significantly poorer in the postassessment. These results are consistent with the findings of two previous Indian studies assessing the effect of CNS prophylaxis on intellectual functioning of children with ALL. A study conducted by Jain *et al*. included 35 ALL children and 20 healthy children aged 5–15 years showed that children with ALL performed significantly poorer in IQ tests when compared to the healthy children. The difference in their mean scores was 13.6, where the children with ALL received a CRT dosage of 20 Gy.[18] In this study, the mean PIQ score among ALL patients significantly decreased from the first assessment to the fifth assessment (mean difference = 11.3). In their prospective and longitudinal study, Abraham and Appaji reported that 19 children with ALL treated with CNS prophylactic therapy in the age group of 6–12 years had a significant decline in their IQ.[19] Another comparative Indian study conducted by Bhattacharya *et al*. revealed that the mean verbal intelligence quotient, PIQ, and full intelligence quotient were comparable between the children who received CNS prophylactic treatment and children with solid tumors who received chemotherapy alone, with the differences not being statistically significant. However, the study reported that the dispersion of IQ scores was greater in the children who received CNS prophylactic treatment with a larger number of patients having scores of <80.[20] Similarly, in this study, only a few children had scores below the average (80–89) across the five assessments, which indicated the difference in intellectual functions between the different phases of treatment protocol. Furthermore, children with ALL did not show significant differences in mean PIQ scores after undergoing the intensive phase of chemotherapy (induction and consolidation phase). However, after the consolidation phase, and CRT, a decline in the mean PIQ scores was observed. This finding is in line with that of Brown *et al*. and Anderson *et al*. who did not find any immediate effect in the intellectual abilities of the children with ALL treated with CNS-directed chemotherapy only.[21,22] Ochs *et al*. conducted a prospective longitudinal study with 43 children with ALL who received CNS prophylactic treatment, and they observed significant deficits in IQ.[23] In line with these results, cross-sectional studies conducted by Anderson *et al*. showed that children receiving CRT and IT-MTX performed very poorly than those in the nonirradiated groups on intellectual abilities.[22] However, CNS prophylactic therapy effects surfaced 1 year after diagnosis (mean days = 510.23) in the present study. Similarly, a review study conducted by Copeland concluded that neuropsychological impairments usually manifest within 1–3 years after cranial irradiation and that deficits are progressive.[17,24]

On the MISIC subtests, when comparing the five assessments, we found that visuospatial ability and processing speed of children with ALL significantly declined at the fourth and fifth assessments when compared to the first and second assessments, after receiving CNS prophylaxis along with HD-MTX. The results showed that the performance of children with ALL was poorer in all five subtests of MISIC at postassessment, as compared with healthy children: visuo-conceptual ability, visuospatial ability, processing speed, perceptual organization, and planning. The performance scores of children with ALL decreased from baseline to postassessment, and the scores of healthy children increased from baseline to postassessment. These results, corroborated by those of many previous studies, reveal that CNS prophylaxis is associated with decline in processing speed.[17-19,24-26] In addition to these functions, nonverbal functions such as visuo-conceptual ability, planning and fine motor skills, and perceptual organization are also affected. Previous reports indicate that children with ALL treated with CNS prophylactic treatment tend to show impairments, as documented by Anderson *et al*.[17,18,21]

In this study, verbal learning, memory, and retention were assessed using the Rey Auditory Verbal Learning and Memory Test (RAVLT). Using RAVLT, we found that verbal retention declined from baseline to postassessment in children with ALL who had received CNS prophylaxis therapy along with HD-MTX. This decline in verbal retention was progressive after the commencement of treatment. It is possible that both CRT and chemotherapy affected performance in this domain. This finding was in accordance with that of Précourt *et al*. and Krull *et al*. who attributed the decline to IT-MTX and CRT.[27,28]

Furthermore, other neurocognitive functions such as motor speed (right and left hand), attention (sustained and focused attention), learning and memory (immediate, delayed, and retention for visual and verbal), visuospatial ability and verbal working memory, and verbal comprehension were not

significantly affected in this study. Of interest, improvements were observed in motor speed, focused attention, verbal and visual learning, and visual immediate memory across the five assessments. Similar findings were noted in a previous study, with no significant decline in motor speed,[29] attention,[30,31] verbal and visual learning, visual memory,[32] visuospatial working memory,[29,30] verbal comprehension,[32] verbal short-term memory,[30] and verbal memory and visual memory.[32]

In this study, compared with the healthy children, the children with ALL had significantly poorer neurocognitive functions such as PIQ, visuo-conceptual ability, visuospatial ability, processing speed, perceptual organization, planning and fine motor skills, verbal comprehension, verbal working memory, visuospatial working memory, verbal immediate memory, verbal delayed memory, and visual immediate memory. In line with these results, Giralt *et al*. reported significant differences between patients with ALL and controls in all domains of neurocognitive functions.[33] Another report described that children with ALL treated with cranial irradiation experienced problems in cognitive and educational abilities compared with healthy controls or children treated with chemotherapy alone.[21,34]

Neuroanatomical deficits, common among childhood ALL survivors, include white matter abnormalities, which may result from the disruption of the myelinization process occurring during childhood because of HD-MTX, which is worsened by whole-brain irradiation. Microangiopathy has also been reported in associated with this treatment. MRI scans performed in this study also revealed abnormalities in brain structure for three children with ALL, and these children had poor performance in PIQ, working memory, visual immediate and delayed memory, processing speed, verbal retention, visuospatial ability, attention, planning and fine motor skills, and verbal comprehension.[35-39] This could be because of white matter changes in the brain.

Although deficits in few of the neurocognitive domains were observed in children with ALL treated with the BFM-95 protocol and the scores were poorer in many of the domains as compared to those of the healthy controls, these deficits could also be because of several other factors. For instance, these patients missed long durations of regular schooling, an academic, environment, and intellectual stimulation during their treatment. We observed that parents of most patients were overprotective; this might have limited the patient's learning opportunities. Further investigation is needed to understand the effect of these aspects on neurocognitive functioning of children with ALL. Long-term investigation or regular follow-up of children with ALL after they resume schooling and comparing their academic performance will provide insight into whether these functions can be resumed to normal (before treatment) over a longer period of time or if the changes are permanent and progressive.

Conclusion

The study results show that treatment with the BFM-95 protocol, which includes CNS prophylaxis along with HD-MTX, affects neurocognitive functions in children with ALL. This protocol had impacted neurocognitive domains such as performance intelligence, processing speed, visuospatial functions, and verbal retention. However, children with ALL had poorer neurocognitive functioning when compared to healthy children. These findings highlight the need for effective, less toxic treatment for patients with ALL and cognitive retraining for patients receiving CNS prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

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