ORIGINAL ARTICLE

Attentional ability among survivors of leukaemia treated without cranial irradiation

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Over 80% of children with acute lymphoblastic leukaemia (ALL) are now long term survivors. It is therefore imperative that the late sequelae of treatment are evaluated and measures taken to minimise any long term toxicity. It has been suggested that children who have received treatment for ALL may experience intellectual deficits.^{1,2} In addition it has become apparent that particular aspects of cognitive functioning are affected, including academic achievement, mathematical ability, abstract reasoning, and memory and attention.^{3–8, 10} The mechanisms underlying this wide array of deficits, however, remain unclear and differences in methodological approach across various investigations into long term sequelae associated with ALL make it difficult to ascertain whether the difficulties are directly related to one another. It could be argued that one underlying deficit may account for the various difficulties witnessed. Attention can be viewed as the fundamental building block of higher order cognitive ability. As such it can be hypothesised that a deficit in the ability to utilise attentional resources effectively could account for the array of neuropsychological deficits witnessed among children who have received treatment for ALL.

Rodgers and colleagues⁷ adopted the neuropsychological model of attention suggested by Mirsky and colleagues⁹ in order to gain a detailed picture of the exact nature of any deficits in attention experienced by survivors of childhood leukaemia. This model of attention considers the subcomponents that comprise this cognitive process and delineates attention into three elements: focus, sustain, and shift. The focus element of attention is further subdivided into focus–encode and focus–execute. Focus–encode requires the individual to target, recall, and then manipulate information. Focus–execute refers to the ability to target information rapidly and efficiently and to then make a subsequent response based on that information. The sustain element is the capacity of the individual to maintain focus over a period of time, namely to maintain alertness or vigilance. Shift refers to the ability of the individual to change the focus of attention in an adaptive and flexible manner.

Background: Previous research has indicated that children who have received treatment for leukaemia which includes cranial irradiation exhibit deficits in their ability to focus attention. It has been suggested that the use of cranial irradiation may have a role to play in long term sequelae.

Aims: To investigate neuropsychological functioning among children treated for leukaemia without cranial irradiation.

Methods: In a cross sectional study, 17 leukaemic patients and their sibling controls were assessed using a neuropsychological model of attention. All were treated on the UKALL XI protocol and none had received cranial irradiation. Participants completed the Arithmetic subtest and Digit Span subtest of the Weschler Intelligence Scale for Children–Revised to assess focus–encode elements of attention; the Coding subtest and the Speed of Information subtest of the BAS to assess focus–execute aspects of attention; the VIGIL computerised battery to assess sustain elements of attention; and the Wisconsin Card Sorting test to assess the ability to shift attention.

Results: These children did not exhibit the deficits witnessed in previous cohorts, and were performing at comparable levels to their controls on all measures of attention

Conclusions: These findings suggest that children who have received treatment for leukaemia without the use of cranial irradiation do not show the neuropsychological insult found in earlier treatment groups.

The Mirsky model of attention is useful for a number of reasons. Firstly, it facilitates a systematic approach to the study of attentional ability. Secondly, the model provides suggestions as to the localisation of function within the brain of the differing attentional factors, which may provide insight into the specific nature of any brain damage experienced by this clinical group. Mirsky and colleagues⁹ suggest areas of the brain thought to be associated with particular attentional abilities; the focus–encode elements were thought to involve the amygdala and the hippocampus, while focus–execute involved more inferior parietal, superior temporal, and striatal regions. They further suggest that the ability to sustain attention is mediated by the reticular formation in the brain stem with some involvement of thalamic structures. Finally they suggest that the ability to shift attention involved frontal lobe functioning. There is a growing body of evidence that provides empirical support for the model.^{10–12}

Utilising this model Rodgers and colleagues⁷ studied attentional ability among a cohort of 19 children in complete continuous remission from ALL, all of whom had received cranial irradiation. Highly specific attentional deficits involving significantly poorer performance on measures of the “focus–encode” and “focus–execute” elements of attentional ability were observed. What was unclear from this study, however, was the cause of this attentional difficulty—that is, whether the aetiology was disease or treatment related. However, in other studies the use of cranial irradiation has been implicated as a cause of the neuropsychological sequelae witnessed.¹³ The conclusions which can be drawn from such research are equivocal as there exists an additional body of evidence which suggests that chemotherapy may account for neuropsychological late effects.^{14, 15}

Abbreviations: ALL, acute lymphocytic leukaemia; BAS, British Ability Scales; CPT, Continuous Performance Task; WCST, Wisconsin Card Sorting Test; WISC-R, Weschler Intelligence Scale for Children (Revised)

Table 1 Age at diagnosis and at assessment and gender of participants in the leukaemia group and their sibling controls.

Group	Males	Females	Age at diagnosis (mth)*	Age at testing (mth)†	Time since treatment (mth)†
Patients	11	6	48.53 [16.39]	116.65 [71–163] [25.41]	60.1 [25–56] [20.4]
Siblings	7	10	Not applicable	138.11 [68–164] [30.85]	Not applicable

*Results expressed as mean (SD).

†Results expressed as mean [range] (SD).

The aim of the present investigation is to identify whether the use of cranial irradiation was the main factor that contributed to development of the long term neuropsychological sequelae associated with ALL. A detailed examination of attentional skills utilising the Mirsky model was adopted, working on the premise that attentional ability is fundamental to more complex cognitive processes and has been identified previously as an area of difficulty for the ALL population. A group of children in complete continuous remission from ALL and who did not receive cranial irradiation as part of their treatment regimen were therefore investigated.

PARTICIPANTS AND METHODS

Seventeen children in long term remission from ALL with 17 sibling controls were recruited from a single treatment centre. All children had presented in the Northern region and were treated at the Royal Victoria Infirmary in Newcastle upon Tyne. The children with ALL were treated according to the MRC-UKALL XI protocol. None of the children had CNS disease at presentation and none received cranial irradiation. The immunophenotype of ALL in two patients was T lineage and the remainder were immunophenotypes as common ALL. Three of the children presenting had a high white cell count (greater than $50 \times 10^9/l$ at presentation). The remainder had a white cell count of less than $50 \times 10^9/l$. The treatment regime involved induction with vincristine, prednisolone, asparaginase, and intrathecal methotrexate. The CNS directed therapy was either high dose intravenous methotrexate at weeks 9, 11, and 13 ($n = 8$) or continuing intrathecal methotrexate at weeks weeks 9, 10, and 11 ($n = 9$). All received two to three intensive treatment blocks and were treated for a total of 100 weeks. All were at least two years from completion of therapy. Table 1 gives further details.

Each child underwent the following tests:

- (1) Arithmetic subtest of the Weschler Intelligence Scale for Children (Revised) (WISC-R)¹⁶
- (2) Digit span subtest of the WISC-R
- (3) Speed of information processing subtest of the British Ability Scales (BAS)¹⁷
- (4) Coding subtest of the WISC-R
- (5) VIGIL¹⁸
- (6) Wisconsin Card Sorting Test (WCST).¹⁹

Focus elements of attention

The arithmetic and digit span subtests tests were utilised to examine the focus–encode elements of attention. They require sequential registration and mental manipulation of information.

The speed of information subtest and the coding subtest were used to examine the focus–execute element of attention. They require the scanning of stimuli to locate a target efficiently and quickly and then the execution of a rapid skilled manual response.

All tests were administered in accordance with the standardised method in the test manual. Raw scores were converted to scaled scores for the purposes of analysis.

All methods employed to measure the focus element of attention are commonly utilised to assess orienting and attentional skills²⁰ and freedom from distractibility,²¹ and are believed by Mirsky and colleagues⁹ to be appropriate methods of assessing this aspect of performance.

The sustain element of attention

In their seminal paper, Mirsky and colleagues suggest using the Continuous Performance Task (CPT) developed by Rosvold and colleagues²² as a measure of sustained attention or vigilance. The current study utilised the VIGIL test battery. This method was selected instead of the CPT for a number of reasons. The age of the participants seemed to suggest that a requirement to sustain attention for a period of seven minutes was more appropriate than the rather lengthier requirements of the CPT of up to 14 minutes. Furthermore VIGIL provides the examiner with substantially more information than the CPT, including information regarding false alarms and omissions. In addition, VIGIL enables the examiner to compare performance across four blocks of trials in terms of reaction time, number of commissions, and number of omissions. These four blocks are not detectable to the participant. This information can help to determine any changes in concentration over time and how these changes may affect reaction time, successful detection of target stimuli, and impulsivity. VIGIL is a computerised test of sustained attention over a prolonged period (seven minutes). The test was administered in accordance with the standardised method in the test manual.

The shift element of attention

Following Mirsky and colleagues,⁹ the Wisconsin Card Sorting Task (WCST) was used to examine the shift aspect of attention. The test requires subjects to apply reasoning ability and to change cognitive strategies in response to a changing environment. Further support for the use of this measure as an appropriate tool for the assessment of the ability to respond flexibly and strategically to a changing environment can be found in the work of Ozonoff and colleagues.²³ The test was administered in accordance with the standardised method in the test manual. Raw scores were converted to scaled scores for the purposes of analysis.

Analysis

Investigation of the results revealed that on many of the measures the results were not normally distributed. It was therefore felt that non-parametric tests would be the most appropriate form of analysis, and the Wilcoxon matched pairs signed ranks test was used as the statistical tool throughout the study. All analyses were two tailed. In addition Glass's d was used to calculate effect sizes for the differences between the means of the two groups on each of the tests.

RESULTS

Focus attention

The arithmetic subtest and digit span subtest of the WISC-R measured focus–encode elements, while focus–execute elements were measured using the coding subtest of the WISC-R

Table 2 Results of the analyses comparing scaled scores of participants in the ALL group with siblings on the four measures of focused attention

Test	Patients* (n=17)	Siblings* (n=17)	Wilcoxon Z score	p value	Effect size
Arithmetic	9.59 (2.72)	10.18 (2.83)	-0.750	0.453	0.213
Digit span	8.53 (2.65)	9.59 (1.70)	-1.73	0.083	0.476
Coding	10.59 (2.03)	11.41 (3.28)	-1.25	0.212	0.301
Speed of info	54.24 (11.27)	55.12 (8.66)	-1.41	0.680	0.088

*Results expressed as mean (SD).

Table 3 Results of the analyses comparing raw scores in the ALL group with siblings on measures across trials for the VIGIL test

Test measure	Patients* (n=17)	Siblings* (n=17)	Wilcoxon Z score	p value	Effect size
Reaction time (ms)	563.94 (50.58)	543.76 (62.35)	-0.10	0.32	0.356
Hit rate	0.76 (0.15)	0.87 (0.15)	-1.86	0.06	0.733
False alarms	0.10 (0.09)	0.07 (0.11)	-1.54	0.12	0.299
Commissions	14.29 (12.63)	10.06 (15.36)	-1.42	0.16	0.301
Omissions	35.24 (21.59)	19.00 (21.60)	-1.86	0.06	0.752

*Results expressed as mean (SD).

Table 4 Results of the analyses comparing scaled scores of the ALL group with sibling controls on measures of the WCST

Test measure	Patients* (n=17)	Siblings* (n=17)	Wilcoxon Z score	p value	Effect size
Errors	94.29 (19.13)	100.24 (19.56)	-1.54	0.12	0.308
Perseverative responses	92.47 (21.96)	94.76 (18.33)	-0.47	0.64	0.113
Perseverative errors	92.24 (21.66)	95.71 (18.15)	-0.78	0.43	0.174
Non-perseverative errors	103.41 (18.05)	104.06 (15.90)	-0.62	0.54	0.038
Conceptual level responses	94.94 (19.42)	100.24 (18.28)	-1.11	0.27	0.281

*Results expressed as mean (SD).

and the speed of information processing subtest of the BAS. The performance of the patient group was compared with that of their siblings. No significant difference was found between the two groups. The data show that the patient group was performing at comparable levels to their sibling controls on all measures of focus attention. Table 2 presents the results of the four tests to examine focus elements of attention.

Sustained attention

Normative data for the VIGIL test has been compiled; it displays very little variation in results across subjects of different ages. For this reason it was decided that comparisons should be made between the raw scores of the leukaemic participants and their controls (table 3). Scores on the VIGIL test were calculated as follows:

- Hit rate—an overall accuracy of target discrimination; calculated by dividing total number of targets correctly discriminated by total number of targets presented
- False alarm—occurs when targets are falsely anticipated; calculated by dividing the total number of errors of commission by the total number of targets presented
- Errors of commission—a frequency measure of incorrect responses
- Errors of omission—a frequency measure of number of targets missed
- Reaction time—the average time from the presentation of a stimulus to the response.

These variables were selected to represent the attentional constructs of interest to the investigation in line with Mirsky and colleagues,⁹ and to allow comparison between the present investigation and that of Rodgers and colleagues.⁷

The data show that the patient group was performing at comparable levels to their sibling controls on all measures of sustained attention.

Attentional shift

The scores of the leukaemia group and their matched sibling controls were compared on measures of the Wisconsin Card Sorting Test (WCST), a measure of the shift element of attention. All scores were standardised according to age appropriate norms, with standard scores having a mean of 100 (SD 15). A conceptual level response score was given if three or more correct responses were given correctly. These variables were selected to represent the attentional constructs of interest to the investigation in line with Mirsky and colleagues⁹ and to allow comparison between the present investigation and that of Rodgers and colleagues.⁷ Table 4 shows the results.

No significant differences were found between the patient group and their sibling controls on any measure of the WCST.

DISCUSSION

This results of this study indicate that children in complete continuous remission from ALL who had received treatment on the UKALL XI and did not receive cranial radiotherapy were performing at comparable levels to their sibling controls on all measures of attention as identified by the Mirsky model. In an earlier study, using the same methodology and comparable numbers of participants, children with ALL whose treatment included cranial irradiation were shown to experience difficulties with the “focus” element of attention.⁷ This suggests that the removal of cranial irradiation from the treatment regimen for this group of children may have reduced the risk of long term neuropsychological sequelae. In

addition the results do not support the suggestion that the disease itself or chemotherapy may have a deleterious effect on cognitive performance.^{14 15}

The data must however be interpreted cautiously. Our sample size was small, although comparable with other studies. It can be seen from the results that there was a non-significant trend for patients to score lower than sibling controls during a number of tasks, and in some instances this difference was close to significance (most notably VIGIL omissions and VIGIL hit rate and digit span). An examination of the effect sizes for these subtests suggests that although the analyses indicate that there were no significant differences between the two groups, a larger sample may have produced significant findings. According to Cohen,²⁴ a value of 0.20 is a small effect size, 0.50 is medium, and 0.80 is a large effect size. Taking this into account we can be relatively confident of the findings across all of the subtests used, with the exception of VIGIL hit rate and VIGIL omissions and the digit span subtest. Here we can see effect sizes of 0.733, 0.752, and 0.476 respectively, which suggests that with a larger sample the results may have reached significance. Careful attention should therefore be given to the development of focus-encode and sustained attention skills among this population of children, and additional studies are needed to investigate these trends further.

The characteristics of the sample studied are comparable with those of other studies.²⁵ Three of our 17 children presented with high whitecell count ($>50 \times 10^9/l$). The expected distribution with a white cell count $>50 \times 10^9/l$ within a sample would be 20%.²⁵ Two of the children had T lineage leukaemia, which has an expected percentage within a population of 10%.²⁵ Approximately half of our sample had received high dose methotrexate and the remainder intrathecal methotrexate. An exploration of the potential effects of these CNS directed treatment modalities was not undertaken here due to the small numbers in each group. The nature of the study precluded the availability of premorbid data. Siblings were therefore used as a comparison group. Using siblings as controls is advantageous compared to using non-related controls in that it allows one to control as far as possible for socioeconomic status and cognitive potential. We cannot predict the long term cognitive development for the children in our study. Attempts to predict academic and intellectual growth as a function of time since treatment have been attempted^{26 26}; however the picture remains unclear. It may be that long term neuropsychological difficulties are not manifest for five or more years after treatment. All children in the present study were at least two years from completion of treatment. Methotrexate has been associated with neurophysiological disturbances, but these were only apparent after three years.^{27 28} Therefore, further long term follow up of this group of children may be indicated to determine if there is any change in cognitive functioning over time.²⁹

Despite these cautionary notes, the present study provides support for research which indicates that the removal of cranial irradiation from the treatment regimen for the majority of children with leukaemia has made a positive contribution towards normal long term intellectual development.^{30 31} This research also emphasises the importance of restricting craniospinal irradiation to high risk groups.

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