

Intellectual function after treatment for leukaemia or solid tumours

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SUMMARY Twenty three children who had been treated for acute lymphoblastic leukaemia (ALL) were evaluated intellectually using the British Ability Scales.¹ Their treatment included early cranial irradiation, intrathecal chemotherapy, and systemic chemotherapy. Nineteen children who had been treated for various types of solid tumours (ST), had undergone related chemotherapy, and had received irradiation to sites of the body other than the cranium were used as controls. In addition, patients' siblings were assessed and their scores statistically corrected to produce a best estimate of the patients' pre-morbid degree of intellectual functioning.

The results showed intellectual deficits after treatment in both patient groups, but these were consistently larger in the ALL group, particularly for the higher functions of intelligence. Intellectual deficit in ALL patients did not show immediately after radiotherapy but became progressively more apparent some time afterwards and particularly in younger children. In contrast, in the ST group, intellectual deficits seemed to diminish over time, and the age at radiotherapy was not a critical factor.

Improving survival rates among children treated for malignant disease have brought an increasing awareness of possible late effects of treatment. Prophylactic treatment of the central nervous system (CNS) has been largely responsible for improved survival among children with acute lymphoblastic leukaemia (ALL), but there is increasing concern that in some children it may result in intellectual deficits.^{2–8} Both cranial irradiation and intrathecal methotrexate, which are currently used for CNS prophylaxis, have been implicated as causes of the apparent deficits. It is difficult, however, to establish whether it is the disease itself, the treatment, or the psychological effects of both on the child and his family that are responsible.

To assess the effects of treatment we compared children who had been treated for and had survived ALL with children who had survived an equally life threatening solid tumour (ST). Treatment for both groups was similar apart from the cranial prophylaxis in the ALL group. Each child was assessed only after treatment was completed which meant that no direct information was available about his degree of intelligence before treatment. Unlike previous studies, however, an estimate of IQ before treatment was obtained using a method based on sibling assessment.

Method

Patients. Twenty three children, 14 boys and 9 girls, who were in remission after treatment for ALL were psychologically tested along with their siblings. At diagnosis the ALL patients ranged from age 16–105 months (mean (SD) 48.5 (24.1)) and at testing from 88–182 months (mean (SD) 119 (25.8)). Their siblings ranged at testing from age 60–190 months (mean (SD) 119 (39.8)). All children had received similar treatment for their leukaemia according to a modified ALGB 6801 schedule.⁹ CNS prophylaxis consisted of intrathecal methotrexate (MTX) (12 mg/m² to a maximum of 12 mg) weekly for 5 weeks and then monthly to a total of 10 injections. Cranial irradiation began 6–8 weeks after the start of treatment and 24 Gy were given in 12 fractions over three weeks.

Nineteen children, 15 boys and 4 girls, who had some other form of malignant disease were tested along with their siblings. At diagnosis their ages ranged from 9–180 months (mean (SD) 74 (47)) and at testing from age 59–214 months (mean (SD) 123 (47)): their siblings ranged from age 35–179 months (mean (SD) 117 (45.6)). The primary diagnosis in these children was Wilm's tumour (3), rhabdomyosarcoma (4), Ewing's tumour (2), non-Hodgkin's

lymphoma (1), Hodgkin's disease (5), neuroblastoma (1), fibrosarcoma (2), and parotid sarcoma (1). All had received intensive cytotoxic chemotherapy and 17 children had received irradiation to sites other than the brain.

Psychological tests. Several of the British Ability Scales¹ were administered in a single one hour session. Children aged over 5 years received the following scales: similarities (SIM) and matrices (MAT) that measure reasoning ability; block design level (BDL) and block design power (BDP) that measure accuracy and speed of spatial ability respectively; recall of designs (RDES), recall of digits (RDIG), delayed visual recall (DVR) that measure different aspects of short term memory; word definitions (WDEF) that measure retrieval and application of knowledge. In addition, children over 8 years old were given the speed of information processing scale (SIP), and those aged between 5 and 8 years were given another scale measuring retrieval and application of knowledge (naming vocabulary (NVOC)). Preschool children were given four scales: RDIG, NVOC, and visual recognition (VREC) measuring short term memory; and verbal comprehension (VCOMP) measuring the application of knowledge.

From these a full scale IQ and an ability profile (a graphic representation of each scale score to show

strengths and weaknesses across different abilities) was determined for each child. Since there is evidence that brothers and sisters do not normally have exactly the same IQ but are correlated around 0.5,¹⁰ an estimate of IQ before treatment was obtained by statistically correcting the sibling score using a method outlined by McNemar.¹¹ By this method the sibling deviation from the mean score is halved so that, for example, the estimate of IQ before treatment of a patient whose sibling's IQ is 120, would be $100 + 20/2 = 110$. Likewise a sibling IQ of 90 would give a patient estimate of 95.

This IQ estimate before treatment was subtracted from the patient's score after treatment to give a change score. The size and direction of the change score depended therefore on the extent to which the score after treatment was greater or smaller than the estimate before treatment (that is, a negative change score resulted where the score after treatment was lower than the estimate before treatment).

Results

Table 1 shows the IQ differences between patients, siblings, and estimates before treatment in ALL and ST groups. To find out whether age at diagnosis and time since diagnosis were important variables, correlation coefficients were computed. The correlation coefficient of age at diagnosis with change scores was +0.327 in the ALL group and +0.058 in the ST group. The difference between these was not significant ($t = 1.28$, $df = 40$). The correlation coefficient of time since diagnosis with change scores was -0.269 in the ALL group and +0.384 in the ST group and the difference between these was significant ($t = 2.203$, $df = 40$, $P < 0.05$).

To look at the results in more detail, and in particular to see whether the ALL group showed a global decline or any specific decline in mental functioning or both, the ALL and the ST ability profiles were statistically compared using a repeated measures analysis of variance outlined by Greenhouse and Geisser.¹² Only the patient-sibling pairs

Table 1 IQ scores after treatment and before treatment estimates in patients treated for acute lymphoblastic leukaemia (ALL) and solid tumours (ST), and their siblings

Group	Mean (SD)	Range	t	P
ALL siblings (n=23)	108.4 (8.9)	93-121	} 3.81	P < .001
ALL patients (n=23)	99.1 (13.2)	72-119		
ALL estimate before treatment	104.3 (4.4)	97-111		
ST siblings (n=19)	107.2 (10.9)	91-130	} 0.856	NS
ST patients (n=19)	104.1 (12.8)	73-127		
ST estimate before treatment	103.7 (5.4)	97-115		

NS=not significant.

Table 2 Change scores (mean and SD) for individual British Ability Scales in patients treated for acute lymphoblastic leukaemia (ALL) and solid tumours (ST) aged over 8 years at testing

Group	British Ability Scales									
	WDEF	SIM	BDL	BDP	MAT	RDIG	DVR	RDES	SIP	
ALL (n = 15)										
Mean	-4.1	-3.6	-9.0	-7.0	-4.7	-2.7	-2.9	-5.9	-5.1	
SD	9.6	8.8	8.5	8.1	5.7	9.0	12.4	9.4	11.9	
ST (n = 8)										
Mean	-3.1	+4.4	-4.0	-3.4	+0.9	-2.0	-4.0	-0.2	+3.1	
SD	11.4	13.6	8.7	8.3	6.2	8.5	6.9	6.8	9.4	

WDEF = word definitions; SIM = similarities; BDL = block design level; BDP = block design power; MAT = matrices; RDIG = recall of digits; DVR = delayed visual recall; RDES = recall of designs; SIP = information processing.

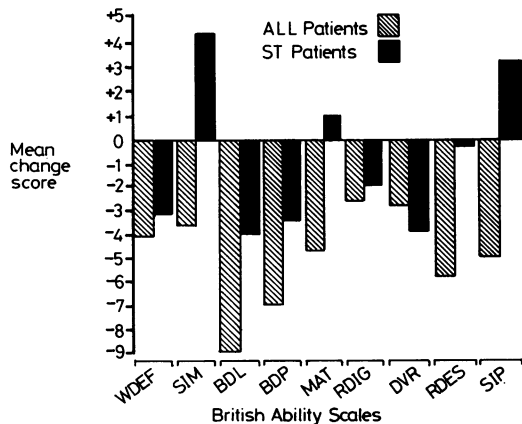


Figure Mean change scores for individual British Ability Scales of patients treated for acute lymphoblastic leukaemia (ALL) and solid tumours (ST) aged over 8 years at testing.

WDEF=word definitions; SIM=similarities; BDL=block design level; BDP=block design power; MAT=matrices; RDIG=recall of digits; DVR=delayed visual recall; RDES=recall of designs; SIP=speed of information processing.

aged over 8 years were used because they had been able to complete a more comprehensive range of scales (see Table 2 and Figure). Neither the differences between groups nor the interaction of groups with tests were significant ($F = 2.4$, $df = 1, 21$; $F = 1.01$, $df = 8, 168$ respectively). There was, however, a trend in the results that suggested that the change scores in the ALL group were more negative than those of the ST group.

Discussion

This study has shown that there is a significant difference between the estimate before treatment and IQ scores after treatment in the ALL but not the ST group. Prophylactic treatment to the CNS may be the causal factor since this was the only major difference between these two groups. Irradiation has been shown to induce a delayed vasculopathy with secondary CNS necrosis.¹³ Price and Jamieson,¹⁴ however, observed a delayed necrosis without evident vascular changes, and suggested that this degeneration occurred only with a combination of intravenously administered methotrexate and 24 Gy of CNS irradiation. They postulated that such a dose alters the property of the blood brain barrier allowing circulating chemotherapeutic agents to diffuse into the CNS and to interfere with the metabolism of the myelin supporting elements.

The size and direction of the correlation of change scores with age suggests that the intellectual repercussions of CNS treatment are greater the younger

the child with ALL is at the time of diagnosis. This is not surprising since the CNS treatment is not directed to any specific site of the brain but to the whole cranium. One may therefore assume that any compensatory mechanism purported by Smith¹⁵ would have been precluded and that the younger brain is more vulnerable.¹⁶

The correlations with time strongly suggest that the decline in IQ after treatment for ALL is larger the longer the time since diagnosis, whereas with ST the decline in IQ is smaller the longer the time since diagnosis. In other words this suggests that the ALL patients are developing at a slower rate than their peers and so over time they are falling further behind them. The ST patients on the other hand may be recovering from the psychological effects of their illness and slowly catching up with their peers.

The ALL group seemed to be showing a decline in almost all the functions of intelligence measured in this study, but in addition to this global deficit some aspects of intelligence seemed to be affected more than others. The scales in which the ALL patients showed particular decline reflect the higher or more complex and integrated functions of intelligence, namely verbal associate reasoning, reasoning with abstract material, fine motor ability in reproducing abstract material, and perceptual analysis and synthesis.

This study differs from others in that it has used a different method to estimate the degree of intellectual functioning before treatment. It is argued that this is better than assuming that patients would normally be functioning at the same intellectual degree as their siblings, as it is well documented that siblings do not usually have exactly the same IQ. It was necessary therefore to correct the sibling scores to account for this and although it is difficult to suggest how best to correct these IQ values, the procedure used here seems reasonable in the light of evidence suggesting that siblings' IQs are correlated 0.5.¹⁰ Indeed, as the results show, without this correction the patient-sibling differences were more significant, so it seems that the effect of this correction is to make a more conservative and, we believe, a more accurate estimate of differences. It should be noted that in comparison with the children used in Eiser's studies³ our children received slightly more intrathecal methotrexate (10 injections compared with 8 or less).

Although CNS prophylaxis has been implicated as the causal factor in intellectual problems after treatment, it seems that it cannot be omitted from treatment. Notice has, however, been taken of results such as these and current regimes now use 18 Gy instead of 24 Gy. Clearly the extent of damage still remains unclear and longer term observation

of these children is therefore necessary to establish this. In addition, the results suggest that damage is not universal and that there may be other causal factors in these deficits (personality factors, and factors at home and at school). A retrospective study such as this cannot hope to identify such potentiating factors since they have all now been affected by the psychosocial effects of being ill and by treatment. There is clearly a need for a long term prospective study to look for such factors in newly diagnosed patients. As a result, particularly vulnerable children might eventually be identified so that remedial help such as the cognitive retraining procedures used by Campione and Brown¹⁷ can be provided to slow or even prevent intellectual deterioration.

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