INTELLECTUAL FUNCTIONS IN CHILDHOOD MALIGNANT DISORDERS

Banani Bhattacharya
R.K. Marwaha
Savita Malhotra
D. Pershad

ABSTRACT

Our study was designed to *compare the intellectual functions in 35 children with lymphoreticular malignancies (ALL or NHL) who had received CNS directed therapy (Group A), with those in 21 patients with solid tumors (Group B). Intellectual assessment was done using the Malin's modification for Indian children of the Wechsler's intelligence scale. Using 5 verbal and performance subscales each, the verbal IQ, performance IQ and full scale IQ were derived. The mean VIQ, PIQ and FIQ were comparable in the. two groups with the differences not being statistically significant. However, the dispersion of IQ scores was greater in Group A with a larger number of subjects having scores of <80. Similarly, the scores obtained in the arithmetic, digit-span, picture completion and block design subscales were lower in Group A. *Mean IQ scores were significantly lower in children over the age of 10 years at diagnosis. Sex, duration since diagnosis, disease free survival and treatment variables did not affect IQ scores. In conclusion, a cross-sectional evaluation of intellectual functions has revealed only minimal differences in children treated with chemotherapy and CNS directed therapy (ITMTX and RT) in comparison to those treated with chemotherapy alone.*

Key words: *Acute lymphatic leukemia, Cranial radiation, Intelligent quotient.*

Survival rates in several childhood malignancies have improved remarkably in the past few decades. Judicious combined modality therapy coupled with excellent supportive care have produced cure rates of almost 90% in certain malignancies(l). Therapy is, however, not without adverse effects. In recent years, the focus of attention has shifted to late effects of treatment. One aspect of these effects is intellectual dysfunction. Central nervous system (CNS) directed therapy, especially cranial irradiation, has been implicated in the genesis of these deficits(2,3). This study was designed to assess the intellectual functions in children who had been treated for malignant disorders.

Material and Methods

Children between the ages of 6 and 15 years on a regular follow-up in the Pediatric Hematology Clinic of Nehru Hospital, PGIMER, Chandigarh, who fulfilled the following criteria were included: *(i)* Group A: cases of acute lymphoblastic leukemia (ALL) or non-Hodgkin's lymphoma (NHL) who had received CNS directed therapy and were in a first complete remission for at least 6 months; and *(ii)* Group B: cases with Hodgkin's disease (HD) or Wilms' tumor (WT) who had completed or were on therapy and were disease free for at least 3 months.

From the Departments of Pediatrics and Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.

Reprint requests: Dr. R.K. Marwaha, Additional Professor, Department of Pediatrics, PGIMER, Chandigarh 160 012.

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Intellectual assessment was done using the Malin's intelligence scale for Indian children (MISIC)(4) which is an Indian adaptation of the Wechsler's intelligence scale for children (WISC). Five verbal and performance subscales each were used. The verbal subscales included information, comprehension, arithmetic, analogies and similarities and digit-span whilst the performance subscales comprised picture completion, block/design, object assembly, coding, and mazes. The verbal, performance and full scale intelligence quotients (IQ) were computed. Marks obtained in recent school examinations were also recorded.

Statistical tests of significance and correlation were applied to determine the significance of the observations.

Results

Thirty-five children with ALL/NHL (Group A) were compared against 21 children with solid tumors (Group B). Boys outnumbered girls in both the groups (71.4% in Group A, 80.9% in Group B). Children between 6 and 9 years formed 57% of the study group.

There were 30 children with ALL and 5 with NHL in Group A while Group B consisted of 19 children with Hodgkin's disease and 2 with Wilms' tumor. The mean interval between diagnosis and intellectual assessment was 29 months (range 6-89) in the former and 21 months (range 3-100) in the latter groups, respectively.

In addition to systemic chemotherapy, all Group A children received CNS directed therapy (intrathecal methotrexate (ITMTX) and cranial irradiation). Twenty-nine received 6 doses of ITMTX each while the rest received 5 doses each. Thirty-two of the 35 received cranial irradiation: 1800 cGy in 30 and 2400/2000 cGy in one each. Children in Group B received only systemic chemotherapy.

The distribution of children according to their socio-economic status (SES) is shown in *Table I.* Though a larger number of children in Group A were from the high SES as compared to Group B, the difference was not significant (Chi square = 4.71, p >0.05).

Marks obtained at school exams are depicted in *Fig. 1.* Around 50% of the children in either group obtained marks between 60 and 80%. One child with ALL obtained above 90% marks whilst 25.7% in Group A and 23.8% in Group B obtained between 80 and 90%. Around 20% of children in either group obtained marks <60% and were rated as below average.

The range of IQ scores in the two groups is shown in *Fig. 2&3.* The mean full scale IQ score in Group A was 99.7 (range 75-118) and 98.2 in Group B

TABLE I—*Socio-economic Status Distribution*

Socio-economic status	Group A		Group B	
	No.	%	No.	%
Low	6	17.2	8	38.1
Middle	16	45.8	10	47.6
High	13	37.0	3	14.3
Total	35	100.0	21	100.0

Chi square = 4.71; p >0.05.

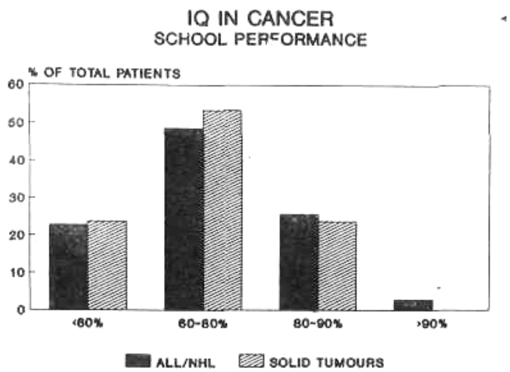

Fig. 1. Scores of school performance.

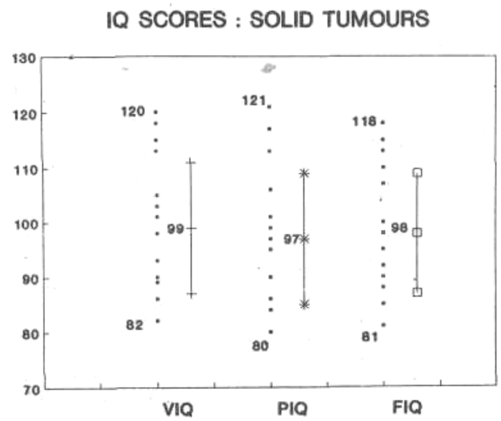

Fig. 3. IQ scores in solid tumors.

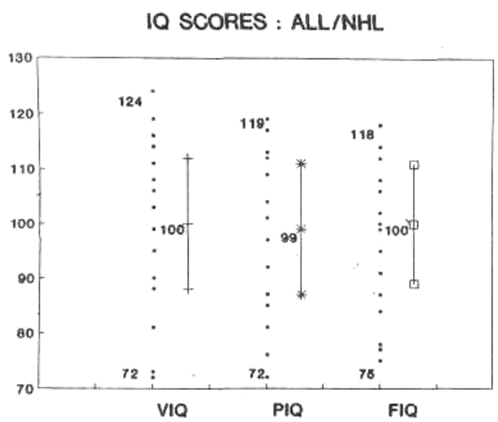

Fig. 2. IQ scores in ALL/NHL.

(range 81-118) (t=0.47, p >0.05). The mean verbal, performance and full scale IQ scores were around 100 in both the groups which is what is expected in a normal population. No differences in scores between the two groups were observed. However, the dispersion of scores was more in Group A and a larger proportion of children obtained scores of <85 (<-1 SD). The n7umbers are too small for any meaningful comparison.

In the subscale IQ tests, Group A children scored less than those in Group B in arithmetic, digit-span, picture completion and block design subscales *(Table II)*. None of these differences were statistically significant. Group A children scored significantly more than Group B children in the mazes subscale (t=2.2, p<0.05).

Among the factors affecting IQ scores, socio-economic status had the most profound influence *(Table III)*. Mean full scale IQ scores were lowest in those from low SES (Group A 84.2, Group B 91.8) and highest in those from high SES (Group A 106.9, Group B 112.6). Significant differences were noted between low and high (t=5.38, p <0.01), middle and high (t=3.7, p <0.01) in Group A and low and high socio-economic groups (t=3.9, p <0.05) in Group B. Again, the differences between the two groups were not significant.

TABLE II-*Subscale IQ Scores*

Subscale	Group A		Group B	
	Mean	Range	Mean	Range
Arithmetic	95	71-120	102.4	85-135
Digit span	90.4	75-113	92.6	80-112
Picture completion	96.2	65-120	98.1	81-119
Block design	102.0	75-153	105.0	75-135

TABLE *III-Mean FIQ Among the Various SE Classes*

Socioeconomic	Group A		Group B	
status	Mean	SD	Mean	SD
Low (A)	84.2	9.11	91.8	8.8
Middle (B)	99.5	8.5	99.0	10.6
High (C)	106.9	8.4	112.6	2.9
t^{A-C}	5.38, <0.001		3.9, P <0.05	
t^{B-C}	2.33, P <0.01		2.1, P >0.05	
t^{A-b}	3.7, P <0.01		1.5, P >0.05	

The mean IQ scores obtained by children in various age groups is shown in *Table IV*. In Group A, children between 6 and 9 years had a mean score of 103.9 while in those between 10 and 15 years it was 95.2 (t=2.09, p <0.05). In Group B, the corresponding scores were 102.4 and 92.5, respectively (t=2.19, p <0.05). The differences in IQ scores in the two age categories between the two groups were statistically insignificant.

Girls, numbering 10 in Group A, obtained full scale IQ scores between *77* and 116 (mean 99.6), whereas boys obtained between 75 and 118 (mean 99.7). In Group B girls, the mean full scale IQ was 98.3 whilst in boys it was 98.1

Nineteen children had disease free survival duration of >2 years (13 in Group A and 6 in Group B). Their full scale IQ scores were in the range of 75 to 118 (mean 97.1) for Group A and 81 to 115 (mean 94.5) for Group B (t=0.4, p >0.05).

Discussion

The present study suggests that significant intellectual deficits have not occurred in 35 children treated with chemotherapy and CNS directed therapy in

TABLE III-*Mean FIQ Scores According to Age*

Age (years)	Group A		Group B	
	Mean	Range	Mean	Range
6-9	103.9	9.7	102.4	10.6
10-15	95.2	12.4	92.5	10.0
T value	2.09, p<0.05		2.19, p <0.05	

comparison to 21 children treated with chemotherapy alone.

A majority of the children in either group had performed well at school as assessed by the marks obtained in school examinations. Though effects in IQ have been demonstrated by several workers, what matters ultimately in practical terms is the ability to keep up with the peer group. In a study on 100 adolescents and young adults (age >16 years) (5) treated for malignancies in childhood (all were well and had ceased therapy), general certificates of education were comparable to the general population of the same age.

In our study, a normal range of IQ scores was seen in both the groups. No difference in scores was seen in children who had received CNS directed therapy as compared to those who had not received CNS prophylaxis. The former scored lesser on the arithmetic, digit-span, picture completion and block design subscales, showing effects in the spheres of perceptual organization and freedom from distractibility(6). However, they performed better in the comprehension and mazes subscales. A normal range of IQ scores has been demonstrated in earlier studies(7-10). However, these scores were significantly lesser than a control group of normal siblings(9,10). It is conjectural whether our patients, who had received CNS directed therapy, would have obtained lesser IQ scores had they been compared with a group of normal children of the same age.

Socio-economic status is known to have a positive correlation with IQ. In our study, too, significant differences in IQ scores were noted in children from different socio-economic classes. Those from a high socio-economic class scored higher than those from a low socio-economic class. However, all children in a particular socio-economic class performed comparably, irrespective of whether they had received CNS directed therapy or not.

Age has been identified, in many studies, as an important factor affecting IQ scores(9-18). In this study, an older age was associated with lower IQ scores. Children between 10 and 15 years scored less when compared to children between 6 and 9 years. The information and object assembly subscales were especially affected. In a majority of the studies, a younger age has been associated with significant intellectual deficits(9-16). However, others(17,18) have found results similar to those obtained in the present study.

No difference in IQ scores was seen in girls as compared to boys in our patients. This is at variance from the findings reported in some studies wherein greater deficits have been observed in girls(9,14,19).

Jannoun, in his study, found a negative correlation between the IQ scores and the time since stopping therapy(8). Similar observations were made by Meadows *et* a/. (10) who found that the drop in IQ scores became evident 3 years or more after diagnosis. Peckham *et* a/. (16) also found that declines in IQ scores occurred 2 to 5 years after therapy and then leveled off. Amongst the few patients in our study who had a disease free survival duration of more than 2 years, no specific differences in intellectual deficits were found.

In most of the reported studies, cranial irradiation had been given in a dose of 2400 cGy. The majority of our patients had received 1800 cGy and 5 to 6 doses of intrathecal methorexate. The lack of significant intellectual deficits in the subjects studied by us could possibly be explained by the lower dose of cranial irradiation. This, however, is too simplistic an explanation. Ochs *et al.(21)* have in a prospective study, demonstrated a statistically significant decrease in mean group scores on neuropsychologic tests in children treated with parenteral methotrexate or 1800 cGy with intrathecal methotrexate. Almost 85% of the children in both the groups had significant decreases in academic achievement, IQ scores, or both.

This study has demonstrated minimal intellectual deficits in children with ALL or NHL who received CNS directed therapy. The findings in this group of patients were comparable to those obtained in children with HD or WT treated with combination chemotherapy with the differences not being statistically significant. However, the cross-sectional design imposes limitations in the relevance of our observations. A larger number of subjects, studied in a prospective manner, with serial evaluations, could provide a deeper insight into the prevalence and nature of intellectual dysfunction in long term survivors of childhood malignancies.

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