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Prediction of Intellectual Deficits in Children with Acute Lymphoblastic Leukemia

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ABSTRACT: Possible predictors of reported lower cognitive functioning in irradiated children with acute lymphoblastic leukemia (ALL) were investigated. Thirty-four subjects, 5–14 years old, with ALL in continuous complete remission and without evidence of current or past central nervous system disease, were examined 9–110 months after diagnosis, using standard measures of intelligence and academic achievement. Subjects with a history of post-irradiation somnolence syndrome were significantly older at diagnosis than nonsomnolent subjects. Intelligence (IQ) was found to be unrelated to history of somnolence syndrome. IQ and achievement were unrelated to age at irradiation, irradiation-examination interval, and radiation dosages. The strongest predictor of IQ by far is parental social class. The importance of controlling for social class differences when searching for treatment effects on IQ and achievement is stressed. *J Dev Behav Pediatr 9:122–128, 1988.* Index terms: *lymphoblastic leukemia, cranial irradiation, somnolence syndrome, intelligence, achievement.*

Prophylactic cranial irradiation and improved chemotherapy have greatly decreased the incidence of central nervous system (CNS) leukemia and increased survival rates in children with acute lymphoblastic leukemia (ALL) in the last 15 years.[1] Interest has shifted to the quality of psychological survival in these children, and particularly to effects of CNS irradiation on intelligence (IQ) and achievement. This paper examines factors that might be expected to contribute to present or future intellectual difficulties in ALL patients. Four have been suggested:

1. *Post-irradiation somnolence syndrome.* Ch'ien et al[2] reported seizures and "learning difficulties," defined as "dull normal intelligence, short attention span and poor recent memory," in children who had a history of somnolence syndrome, but not in children without such a history. This syndrome is characterized by drowsiness and lethargy occurring 3–8 weeks after the end of cranial irradiation[3] and was first observed by Druckmann[4] in children receiving low dose cranial irradiation for tinea capitis.
2. *Age at irradiation.* The younger, incompletely myelinated brain may be more vulnerable to irradiation.[5] Three reports have demonstrated a relationship between young age at irradiation and low IQ;[6-8] four have failed to demonstrate a significant relationship.[9-12]
3. *Irradiation-examination interval.* Intellectual performance has been reported to be significantly diminished 3 years, but not 1 year, after irradiation.[13-15] In contrast, no significant correlation between long irradiation-examination interval and IQ was found by Robinson et al[12] in which the mean interval was 7.2 years.

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4. *Radiation dosage.* Supposing that radiation damages the brain, it is logical to hypothesize poorer outcome in patients receiving more radiation. No correlation between radiation dosage and measures of IQ, visual-motor integration, attention, concentration, or short-term memory has been found in two previous studies.[10,16]

The present study was undertaken to examine the effects of somnolence syndrome, age at irradiation, irradiation-examination interval, and radiation dosage on IQ and academic achievement of children with leukemia in continuous, complete remission. This study differs from previously published reports in that (a) it includes a total patient population selected only for age at examination, (b) the same measures are used in all subjects, (c) it excludes subjects with other possible causes of low IQ, and (d) it statistically controls for social class differences.

METHODS

Sample

The subjects of this study included *every* patient with acute lymphoblastic leukemia (ALL) who was (1) between the ages of 5 and 14, (2) without evidence at any time of central nervous system (CNS) or systemic relapse of leukemia, and (3) without history of CNS disease (including encephalitis, meningitis, and seizure disorders), or Down syndrome. Of 43 children meeting the first two criteria, four were excluded because of central nervous system (CNS) disease or Down syndrome leaving 39 who met all three criteria (including one child who had a single febrile seizure in infancy, years prior to diagnosis). Thirty-three were fully studied: one child, age 5, refused to talk but completed nonverbal psychometric tests; four parents completed a behavioral questionnaire (not reported on here) only; and one family refused to participate at all. Twelve of the 39 subjects were still receiving chemotherapy at the time of examination. All subjects attended the Pediatric Hematology-Oncology Clinic in the Babies Hospital of the Presbyterian Hospital in the City of New York, or an affiliated hospital. Subjects were treated with Children's Cancer Study Group Protocols 101, 141, 141a, 161, 162, 163, or 905.[17-23] Subjects were 14–139 months old at diagnosis (mean 60.1, median 55.5) and were examined 9–110 months (mean 49.0, median 45.0) later. All had been irradiated (1800 or 2400 rads) within 2 months of diagnosis. Therefore, in this report, "time since diagnosis" and "time since irradiation" are virtually equivalent. A minimum interval of 6 months between diagnosis and examination was chosen on the assumption that most children will have recovered from the acute illness and returned to school by that time.

Measures

1. *Psychometric testing.* Subjects were tested by experienced psychometricians who knew that the children were in continuous complete remission but were blind to the hypotheses of the study and to history of somnolence, age at irradiation, and radiation dosage. An age-appropriate Wechsler intelligence test (WISC-R,[24] or WPPSI[25]) and the reading comprehension, spelling, and mathematics subtests of the Peabody Individual Achievement Test[26] were administered.
2. *Social class.* The Hollingshead Four Factor Index of parental education and employment was used to determine social class (social class: 1 = highest, 5 = lowest).[27]
3. *Assessment of somnolence.* Each subject's chart was searched for symptoms of somnolence syndrome[2,3] in the notes that had been recorded at weekly to monthly clinic visits during the 4 months after the start of cranial irradiation. If the child was rehospitalized during this period, daily progress and nursing notes were reviewed. A diagnosis of somnolence syndrome was made if the examining physician had specifically noted the presence of the syndrome or if the words "drowsiness" or "lethargy" or a synonym of these appeared in the record during the third through eighth weeks after the end of cranial irradiation. We excluded symptoms of somnolence occurring before the third week (three cases, of which two occurred during the course of irradiation and one after), as well as symptoms which could be attributed to other causes, e.g., intercurrent infection or drug side effects. In no case did somnolence symptoms begin after the eighth week, but in five cases, symptoms persisted beyond the eighth week.

Procedure

Informed consent was obtained from a parent in the presence of the child. Psychometric testing and other measures (to be reported elsewhere) usually were completed in a single morning or afternoon session. Children were not tested on a day when lumbar puncture or bone marrow examination was scheduled, and psychometric testing usually preceded other measures.

Medical records were surveyed twice for symptoms of somnolence syndrome and the abstracts were checked for accuracy. Assignment to the somnolent or nonsomnolent groups was made from the abstracts independently by three of us (PT, CE, AC) who were blind to the identity of the subject and psychometric test results, but not to age at diagnosis or radiation dosage. Where disagreement occurred (11 of 34 cases), we reviewed abstracts and medical records together and reached a consensus, in every instance rating doubtful cases as nonsomnolent. This procedure was therefore weighted toward assigning nonsomnolent ratings.

Data Analysis

Histograms were plotted to assess the distribution of continuous variables, and scatterplots were inspected to evaluate the possibility of nonlinear relationships between variables. Z-tests for point estimates when population means are known were used to determine deviance from population norms. Chi-square tests were used for categorical data, two-tailed t-tests and Pearson product-moment correlations for continuous variables, and multiple regression analyses were used to partial out the effects of several different factors measured. In addition, in the regression of IQ on radiation dosage and age at irradiation, we included as an independent variable an interaction term, namely, the product of rads and age at irradiation.

RESULTS

Inspection of the histograms demonstrated sufficient variability and distributions appropriate to satisfy the assumptions of normality for statistical procedures. Inspection of scatterplots of full scale, verbal, and performance IQ (FSIQ, VIQ, PIQ) against the continuous variables of socioeconomic status (SES), age at irradiation, and follow-up interval revealed only linear relationships between the various dependent and independent variables.

Cognitive Functioning of the Entire Sample

This study was not designed and is not intended to assess whether as a group, children with acute lymphoblastic leukemia (ALL) exhibit cognitive deficits. However, it is of some interest to compare the cognitive functioning of this sample to available normative data. Mean FSIQ (98.5 ± 19.2), VIQ (98.6 ± 20.1), and PIQ (98.9 ± 18.9) in this sample were not significantly different than population norms ($\mu = 100 \pm 15$). Of the 10 subtests of the Wechsler intelligence tests, only information ($\bar{x} = 8.6 \pm 4.0$) and arithmetic ($\bar{x} = 8.8 \pm 3.0$) were significantly different ($p < 0.01$) from population norms ($\mu = 10 \pm 3$). There was no difference between this sample and population norms on reading achievement ($\bar{x} = 99.9 \pm 15.3$; $\mu = 100 \pm 15.3$; $\mu = 100 \pm 15$), but arithmetic ($\bar{x} = 95.1 \pm 15.8$) and spelling ($\bar{x} = 94.2 \pm 15.9$) achievement were both significantly lower.

Socioeconomic Status

The mean SES of the entire sample was 2.6 ± 1.3. Social class was highly correlated with all three measures of IQ (VIQ: $r = -0.67$, $p < 0.001$; PIQ: $r = -0.31$, $p < 0.05$; FSIQ: $r = -0.60$, $p < 0.001$).

Somnolence

Of the 39 subjects who met inclusion criteria, 18 (46%) were rated somnolent. These subjects were significantly older when irradiated than nonsomnolent subjects [75.4 ± 33.8 vs 52.6 ± 25.3 months, $t(37) = 2.41$, $p < 0.05$] but did not differ in age at examination (117.7 ± 37.4 vs 105.1 ± 31.2 months), follow-up interval (42.9 ± 25.8 vs 52.4 ± 24.9 months), radiation dosage (2106 ± 305 vs 2187 ± 285 rads), or sex distribution (56% vs 52% male). Although not statistically significant, there were more lower social class subjects [Hollingshead class IV, V) in the nonsomnolent (6/18) than somnolent (3/16) groups [χ^2 (1 df) = 0.33, $p < 0.54$]. Three nonsomnolent and two somnolent subjects refused psychometric testing; subsequent analyses are based on 34 subjects.

Table 1 shows a 13-point difference in VIQ between somnolent and nonsomnolent groups. This difference only approaches significance [$t(31) = 2.00$, $p < 0.06$], and is in the opposite of predicted direction, the somnolent group having a higher VIQ. Other IQ and achievement test differences are also nonsignificant.

If young age at irradiation predicts later cognitive problems, lower VIQ might have resulted from the younger age at irradiation of nonsomnolent subjects. In an analysis of covariance, controlling for age at irradiation, higher VIQ remained nonsignificantly related to somnolence ($F_{1,29} = 2.92$, $p < 0.10$).

Age at Irradiation and Irradiation-Examination (Follow-up) Interval

Because we chose to examine subjects at least 5 years old, children who were older at diagnosis are likely to have shorter follow-up intervals. Therefore, these two variables are related to each other ($r = 0.31$, $p < 0.05$), but their independent contribution is considered here. The Pearson product-moment correlations of IQ and age at irradiation and follow-up interval are shown in Table 2. No significant relationship was found. Achievement scores were not significantly correlated with age at irradiation or follow-up interval.

Radiation Dosage

Radiation dosage was dichotomized (high = 2400 rads, low = 1800 rads). Higher dosage was weakly (nonsignificantly) correlated (point biserial) with lower IQ scores (Table 2), and was unrelated to achievement scores. We

TABLE 1. Somnolence, IQ, and School Achievement

	Nonsomnolent (n = 18)		Somnolent (n = 16)	
	$\bar{X}$	SD	$\bar{X}$	SD
VIQ[a]	92.1[b]	21.1	105.4	16.9
PIQ[a]	98.7	21.9	99.3	15.6
FSIQ[a]	94.5[b]	21.4	102.7	16.3
PIAT reading				
Comprehension[c]	97.8[d]	17.2	102.3[d]	12.9
Mathematics[c]	91.1	17.5	99.6	12.6
Spelling[c]	92.2	15.6	96.3	16.6

[a] WISC-R or WPPSI.
[b] n = 17.
[c] Age standard scores.
[d] n = 15.
All differences nonsignificant. Abbreviations: VIQ, verbal IQ; PIQ, performance IQ; FSIQ, full-scale IQ; PIAT, Peabody Individual Achievement Test.

TABLE 2. Pearson Correlations of IQ and Achievement with Age at Irradiation, Follow-up Interval, and Radiation Dosage and Social Class

		Age			
	n	Irradiation	Follow-up[a]	Rads	SES
VIQ[b]	33	0.174	−0.246	−0.225	−0.672[c]
PIQ[b]	34	0.125	−0.118	−0.181	−0.319[d]
FSIQ[b]	33	0.188	−0.219	−0.189	−0.600[c]
PIAT reading					
Comprehension[e]	33	0.065	0.186	−0.138	−0.559[c]
Mathematics[e]	34	0.153	0.070	−0.069	−0.511[f]
Spelling[e]	34	0.051	0.110	−0.165	−0.544[c]

[a] Follow-up = age at examination minus age at irradiation.
[b] WISC-R or WPPSI.
[c] $p < 0.001$.
[d] $p < 0.05$.
[e] Age standard scores.
[f] $p < 0.01$, all other correlations nonsignificant.
Abbreviations: SES, socioeconomic status; VIQ, verbal IQ; PIQ, performance IQ; FSIQ, full-scale IQ; PIAT, Peabody Individual Achievement Test.

found no interaction between radiation dosage and age at irradiation.

Finally, to assess the relative importance of the various factors that have been reported to contribute to lower IQ, we conducted four two-variable stepwise regression analyses. In each regression equation, VIQ was first regressed on SES, the variable with, by far, the strongest zero-order relation to IQ. SES accounted for 45% of the variance in VIQ (Table 3). In step two, one of four variables (somnolence, age at irradiation, follow-up interval, rads) was entered. This method allows one to assess the relative importance of each variable in predicting VIQ. None of the four step-two variables accounted for significant additional variance in VIQ after SES was entered. Somnolence approached significance but in the opposite of expected direction ($F_{1,30} = 3.93$, $p = 0.057$). The four two-variable stepwise regressions were repeated using PIQ and FSIQ as the outcome. Again, no significant additional variance was found.

TABLE 3. Two-step Regression: R^2 Increase in IQ After Controlling for SES

	VIQ (n = 33)	PIQ (n = 34)	FSIQ (n = 33)
Somnolence	0.064[a]	0.001	0.019
Age at irradiation	0.014	0.024	0.019
Follow-up interval	0.042	0.024	0.034
Rads	0.033	0.003	0.016
R^2 for SES alone	0.451[b]	0.153[c]	0.360[b]

[a] $p = 0.057$.
[b] $p < 0.001$.
[c] $p < 0.05$, all others nonsignificant.
Abbreviations: SES, socioeconomic status; VIQ, verbal IQ; PIQ, performance IQ; FSIQ, full-scale IQ.

DISCUSSION

This study examined four factors which may contribute to intellectual deficits in children treated for acute lymphoblastic leukemia (ALL): somnolence syndrome, age at irradiation, follow-up interval, and radiation dosage. The subjects included a total clinic population of irradiated ALL patients in continuous complete remission who were 5–14 years old at the time of examination, excluding only those patients whose intellectual abilities might have been lowered by factors other than those under study, such as central nervous system (CNS) or systemic relapse (with added chemotherapy and/or CNS irradiation), seizures, or Down syndrome. The same psychological measures were used on all subjects, and social class was statistically controlled for. Only one[28] of the previously published studies examined the *relative* contribution of possibly deleterious factors (social class and age at diagnosis) to outcome as this report does.

We could not confirm the direct relationship between somnolence syndrome and "learning difficulties" as reported by Ch'ien et al,[2] a finding also unconfirmed by other studies.[29,30] Because our information on somnolence syndrome was derived from retrospective record review, it is possible that some misclassification took place. However, our somnolence rate of 46% is similar to that reported in nine other studies (overall mean for 698 subjects: 43%, range 10–78%)[2,3,29-30] and to the 51% rate reported for prospective studies only (range 36–66%).[2,29-32,34] We might expect that if misclassification was obscuring a real relationship between somnolence syndrome and intelligence (IQ), than a comparison of cases with positive chart notation of somnolence syndrome ($n = 7$) to cases free of somnolence symptoms ($n = 17$) (thus excluding ambiguous cases) might yield a significant difference. This analysis approaches statistical significance, but in the opposite of predicted direction. Specifically, somnolent subjects had higher verbal IQ (VIQ) (109.3 vs 92.1, $t = 1.98$, $p < 0.06$) and were significantly older (78.7 vs 50.6 months, $t = 2.2$, $p < 0.05$) than nonsomnolent subjects.

Neither did we find significant differences between somnolent and nonsomnolent subjects on achievement measures. A more recent report by Ch'ien's group,[29] with a much larger sample size, shows similiar means and standard deviations and no significant differences between somnolent and nonsomnolent groups. Perhaps the discrepancy between our results and those of Ch'ien et al,[2] in their original paper, can be accounted for by the latter's inclusion of one subject who developed leukoencephalopathy after treatment with high dose intravenous methotrexate and cranial irradiation (Ch'ien, 1980, personal communication).

We did not find lower IQ in subjects who were younger at irradiation or had longer follow-up intervals. The literature on these factors is far from consistent. Although three of the better-controlled studies found lower IQ in younger irradiated subjects,[6-8] others have failed to demonstrate a significant relationship.[9-12] Reports of lower IQ in longer irradiation-examination interval subjects[12-15] are unreliable, in that follow-up interval and age at irradiation are confounded. None of these studies controls for social class or age at irradiation differences. It is possible that there are delayed effects on IQ which subside over time. We found no obvious nonlinear pattern in the scatterplot of IQ versus follow-up interval, but since this study is not longitudinal, it is possible that the interindividual variations in IQ would obscure a pattern that would emerge in longitudinal data.

We found a nonsignificant trend for higher radiation dosage to be associated with lower IQ, but young age at irradiation and high radiation dosage do not appear to interact. Examination of a larger sample of low- and high-dose subjects would be valuable. If such a study substantiated an inverse relationship between radiation dosage and IQ, a switch to lower radiation dosage treatment regimens would be indicated, since CNS prophylaxis with 1800 rads has been shown to be as effective as with 2400 rads.[36]

As noted above, this study was not designed to assess whether treatment of ALL leads to cognitive deficits. To study this issue, ideally one would need prediagnosis IQ and achievement data. This is impractical, because it would require testing an extremely large number of children to obtain a cohort who eventually developed this rare disorder. Postdiagnosis but pretreatment test results

would not necessarily reflect the premorbid functioning of these severely ill children. Premorbid school records would be of interest, but would vary from school to school. Further, many newly diagnosed children have not yet attended school.

In the absence of premorbid data, an appropriate comparison group would allow assessment of the effect of leukemia and its treatment on cognitive functioning. Unaffected siblings might serve as a control group for family influences of heredity and environment. Children with other forms of cancer who do not receive intrathecal medication or cranial irradiation might serve as controls for effects of illness and missed school. These control groups have been utilized in other studies which were specifically designed to assess whether there is a cognitive deficit caused by this disease.

The currently available literature about the effects of cranial irradiation on IQ is not consistent. Whereas a few studies demonstrate lower IQ in irradiated leukemic children than in nonirradiated controls,[6-7,16,37] a greater number do not.[6,10,12-13,28,38-44] (The negative studies are generally, but not uniformly, less well-designed.) Some studies that purport to show IQ differences include subjects with CNS leukemia and systemic relapse,[44-45] or do not clearly exclude subjects with other possible cause for low IQ, such as seizures or encephalopathy.[9,37]

In the present study, no control group was utilized, since it was designed to assess the effect of several treatment factors within a total patient population. Comparison of the data from this sample to population norms should be interpreted with caution. Cognitive functioning in leukemia patients can be adversely affected by treatment and yet not fall below normal range. If, for some reason, the patient population is biased toward higher premorbid levels of cognitive functioning, even substantial declines from premorbid levels could result in "normal" test scores. The present sample provides an example of such a possible bias. The mean social class of this sample (2.6 ± 1.3) is significantly higher than in the general population ($\mu = 3.7 \pm 1.0$, $p < 0.001$). The unstandardized regression coefficients from a regression analysis of IQ on socioeconomic status (SES), age at irradiation, and somnolence indicate that in this sample, a decrease of one level of SES leads to an 8.7-point decrease in full scale IQ (FSIQ) and a 10.0-point decrease in VIQ. As the sample mean SES is approximately one level higher than the population mean, we might expect sample mean IQ to have been higher than the population mean IQ at baseline. The fact that, after treatment, the sample IQ mean is slightly lower than population norms could represent a decline in intellectual functioning. Without premorbid data or appropriate age, SES, and treatment-matched controls, it is not possible to say what overall effect, if any, treatment has had on these subjects.

We found that our subjects scored significantly lower than population norms on information and arithmetic subtests of the Wechsler scales and on Peabody arithmetic and spelling achievement tests, but not reading comprehension. The available literature shows no consistent pattern of deficiencies in Wechsler subtests[6,40,41] or achievement tests (three reported no differences from controls,[38,41,43] one reported lower WRAT arithmetic but not word recognition or spelling,[40] and one reported superior arithmetic achievement) in irradiated versus nonirradiated leukemic subjects.[28] Again, our study was not designed to evaluate this issue, and further research needs to be done on the pattern of deficits in these children.

We wish to emphasize the importance of controlling for social class (as measured by parental education and occupation) in this research area. In our sample, children of social classes 4 and 5 had significantly lower VIQ and FSIQ than subjects in social classes 1, 2, and 3. Parental social class is a good predictor of a child's IQ and achievement.[46] It is easy to see how nonrandom distribution of social class can bias cognitive findings in a small sample. Most reports do not control for social class;[9,10-14,16,30,38-45,47,48] only Moss et al,[6] Eiser,[7] Eiser and Lansdown,[8] Whitt et al,[28] and Jannoun[37] do.

A methodological difficulty that affects the present study is its small sample size. Since the sample represents a total patient population in the given age range, biases present should be limited to those introduced by the selection by age. Although there are children in the sample who were diagnosed and irradiated when as young as 14 months old, there are no recently diagnosed children who are younger than 5 years old. However, IQ assessment below the age of 5 is not reliable, and available instruments do not correlate well with Wechsler scales. The sample is too small to explore adequately the effects that this age restriction introduces. However, since there is a complete range of age at diagnosis and irradiation, bias will hopefully be minimal and not affect the interpretation and generalization of positive findings.

More problematic is the interpretation of negative findings. Lack of statistical significance at $p = 0.05$ level does not prove the null hypothesis. The sample size in this study provides us with a power of 0.80 to detect a 15-point (one standard deviation) difference between group means in IQ and achievement t-tests. However, smaller group differences of 10 or even 7.5 points could be clinically important. In this study, we only have power of 0.28 on t-tests and 0.30 on regression analyses to detect differences between groups of 7.5 IQ points. This is clearly inadequate. A sample size of 126 subjects (63/group) would be required to detect a 7.5 IQ-point difference with a power of 0.80. Such a sample size will require a multicenter study.

In summary, our data support previously published reports that postirradiation somnolence syndrome does not predict later cognitive dysfunction. Somnolence is more frequently observed in older children. The data do not support young age at irradiation or longer diagnosis-examination interval as predictors of cognitive dysfunction. The trend toward lower IQ in children receiving higher radiation dosages bears further investigation. Our data, which show the powerful contribution of social class to cognitive outcome, cast doubt on other reports of irradiated leukemia patients which fail to control for social class differences among subjects and control groups. Despite the logistic difficulties inherent in such work, multicenter research is advocated to obtain sample sizes that provide adequate power to detect important effects on IQ and academic achievement.

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