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Post-treatment intellectual functioning in children treated for acute lymphoblastic leukaemia (ALL) with chemotherapy-only: A prospective, sibling-controlled study

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ABSTRACT

Intellectual functioning (verbal, performance and full-scale IQ) in 43 children treated for acute lymphoblastic leukaemia (ALL) with chemotherapy-only was evaluated in a nationwide, prospective, sibling-controlled study. Intellectual assessment was performed at diagnosis and repeated shortly after cessation of 2 years treatment, including intrathecal and systemic chemotherapy. Using hierarchical regression analysis, patients' and siblings' ($n = 27$) scores were longitudinally analysed and compared to assess possible changes and differences over time. At both assessments, before and after treatment, patients showed average scores on intelligence tests compared to population norms. Longitudinal analysis and cross-sectional comparisons revealed no significant differences between patients and controls. Young patients showed a small relative decline, albeit not significant, on performance-IQ compared to healthy siblings. Despite intensive and potentially neurotoxic treatment, no evident negative effects on intelligence were found. However, it cannot be precluded that younger patients are at risk for a small decline in PIQ.

1. Introduction

Acute lymphoblastic leukaemia (ALL) is the most common form of childhood cancer with a cure rate approaching 80%. To achieve this good outcome, prophylactic treatment of the central nervous system (CNS) in addition to systemic chemotherapy is essential.[1,2] Former treatment protocols using cranial radiation (CR) as prophylaxis have shown lower intelligence scores and specific neuropsychological deficits post-treatment in patients compared to controls.[3–5] To avoid these adverse late effects, children with ALL have been treated with chemotherapy-only regimens since the early 1980s.

While patients treated with chemotherapy-only perform better on intelligence tests than those who received CR,[6–8] it is yet unclear if the intellectual achievement in the former patients is equal to healthy peers. In a recent review by Moore, it

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was concluded that studies of the effects of chemotherapy in isolation are far less frequent compared to the effects of CR on cognitive outcome.[9] Some studies report lower scores on intelligence tests compared to controls,[10,11] while others find no deterioration of intellectual abilities over time.[12,13] Methodological problems including lack of proper control groups, missing base-line assessments prior to treatment, limited age range, test-shift and small sample size may have added to the inconsistent results found in the chemotherapy-only late effect studies.[14–16]

To overcome such methodological problems, we started a nation-wide, prospective sibling-controlled study, in which patients were assessed with Wechsler intelligence scales within two weeks after the start of chemotherapeutic treatment and after cessation of therapy. We recently showed that testing of patients shortly after diagnosis is feasible and reliable.[17] In that study, no adverse effect of illness and psychological stress on the IQ of patients with recently diagnosed ALL was found. In the present report, we focus on the patients' intellectual functioning over time until shortly after cessation of treatment, in comparison to their base-line performance and to sibling-controls.

2. Patients and methods

2.1. *Subjects*

From 1999 to June 2001, 85 consecutive patients from six paediatric oncology centres in the Netherlands were eligible for the study. Inclusion criteria for this study were newly diagnosed children with ALL, age between 4.0 years and 12.3 years, and Dutch as their primary language. The age criterion was chosen because the follow-up time was 4.6–5.0 years (two windows of 3 months for two re-assessments). Most psychometric tests for children and youngsters can be used till the age of 17; hence, the upper age threshold at the time of inclusion could not exceed 12 years. Patients with initial CNS leukaemia or pre-existent disorders that could interfere with normal cognitive development were excluded. Sixteen out of 85 parents refused to participate because of the expected burden and 19 patients did not enter the study due to a long absence of the referring psychologists in two centres. Those two psychologists should have referred the patients in two of the participating hospitals to the single neuropsychologist who had done all assessments. Fortunately, a very low number of patients were lost during follow-up. The 50 participating children represented 59% of potentially eligible patients and did not differ significantly from non-recruited children with regard to age, gender, SES and disease characteristics. Moreover, the missing patients from the two afore-mentioned centres did not differ from the national cohort of paediatric leukaemia patients.

Twenty-nine patients had healthy siblings who could serve as a control with the same inclusion criteria as the patients with respect to age, language and normal development. If a patient had more than one eligible sibling, the child closest in age to the patient was chosen. The characteristics of patients and sibling controls are given in Table 1. Parental informed consent was obtained according to the institutional rules. Full details of the group of children included in the first neuropsychological assessment (NPA-I) were described in Jansen and colleagues.[17]

Measurements could be repeated in 44/50 patients, but only 43 were included in the analysis. Reasons for attrition were relapse of ALL or death ($n = 3$), refusal to further participation ($n = 2$), or switch over to another treatment protocol ($n = 1$). Retrospectively, there were strong indications for premorbid mental retardation in one child, who could not complete the intelligence test at NPA-I. After the second neuropsychological assessment (NPA-II), it was decided to exclude this patient from the study, so that an aggregate group of 43 patients who were in complete continuous remission could be assessed twice. To preclude any bias, we excluded the results of 11 patients who had incomplete IQ tests at the first assessment from the longitudinal analysis but these children could be re-subjoined in the post-treatment comparison with the siblings. Mean FS-IQ at NPA-II of these patients was lower (101.3), compared to the main patient group, but these relatively lower scores were caused by only two individual patients who had an IQ < 90. The 32 patients who

Table 1 – Numbers and characteristics of patients and siblings

	Patients	Siblings
Base-line inclusion[17]	50	29
Incomplete IQ measures at NPA-I	(11[a])	(0)
Drop outs	7	2
Longitudinal analysis (*N* total)	32	27
Longitudinal analysis (>6 years at NPA-I; analysis 1)	21	21
Median age at diagnosis (range)	7.6 (6.2–11.7)	8.3 (6.8–12.6)
Female (%)	38	57
Longitudinal analysis (<6 years at NPA-I; analysis 2)	11	6
Median age at diagnosis (range)	5.0 (4.0–5.9)	5.6 (4.5–5.9)
Female (%)	18	67
Cross-sectional, post-treatment analysis (all ages; analysis 3) (32 + 11[a])	43	27
Median age at diagnosis (range)	6.4 (4.0–11.7)	8.2 (4.5–12.6)
Female (%)	41	62

a Patients who had incomplete measures at NPA-I but full measures at NPA-II and then added to the post-treatment analysis.

were included in the longitudinal analysis were comparable in respect to age, gender and disease characteristics to the rest of the study population. Of the 29 siblings, 2 (7%) refused to participate at the NPA-II; hence a total of 27 could be assessed.

2.2. Treatment

Patients were treated according to the national chemotherapy-only Dutch Childhood Oncology Group (DCLOG) ALL-9 protocol, including systemic chemotherapy (vincristine, dexamethasone, L-asparaginase), medium dose methotrexate (MTX), 6-MP and repeated triple IT (MTX, PD, ara-C) therapy as CNS prophylaxis. This protocol is similar to the DCLSG ALL-6 protocol.[18–20] High risk patients (16/50) received additional systemic chemotherapy including daunorubicin, cyclofosfamide and cytosine-arabinoside. All patients had received one dose of vincristine, dexamethasone (daunorubicin in case of high risk patients), and triple IT therapy before their first assessment. The total duration of treatment was 108 weeks.

2.3. Study design

At NPA-I, patients were individually evaluated within two weeks after diagnosis. Siblings were individually assessed within four weeks after the patients' evaluation.[17] NPA-II was repeated for three to six months after cessation of therapy, that is, 2.3–2.6 years after NPA-I (Md = 2.4 years).

To optimise standardisation, all participants were tested nationwide by one qualified child neuropsychologist. The patients were tested either at home or at the hospital but no difference in IQ-scores was found between these two sites.

2.4. Test materials and procedures

At NPA-I, not all children could be tested with the same IQ-test. Children aged 4–6 years were assessed with the Experimental Dutch-Flemish version of the Wechsler Pre-School and Primary Scales of Intelligence (WPPSI-R) (10 subtests; extrapolating for the subtests comprehension and geometric design).[21] The children $\geqslant$6 years were tested with the Wechsler Intelligence Scale for Children-revised (WISC-R, Dutch version) (10 subtests; extrapolating for the subtest comprehension and picture arrangement).[22] At NPA-I, the patients ($N = 11$) who missed >2 subtests were excluded from the longitudinal analysis. The reasons for missing data were an infusion in the (dominant) hand, illness, pain, tiredness or a combination of these factors. At NPA-II, all children were tested with the WISC-R. Twenty-one patients and 21 siblings were assessed twice with the WISC-R. For the WPPSI-R and for the WISC-R, mean norm-scores are 100 (SD = 15).

2.5. Statistical methods

To compare the patients with siblings, regression analyses were preferred to more traditional ANCOVA because an interaction effect between the age and group was expected. Moreover, this statistical technique is often used such that a stepwise control could be performed for possible confounding effects.[23]

We conducted three different analyses (Table 1). First, longitudinal comparisons were made by hierarchical regression analysis for the group of patients and siblings who were assessed with the same test (WISC-R) at both NPA-I and NPA-II. In this model, the differences between NPA-II and NPA-I for FS-IQ, verbal IQ (VIQ) and performance IQ (PIQ) performances were predicted with age, group and interaction between age and group as explanatory variables.

Second, data of a subgroup of patients and siblings who had been tested with the WPPSI-R at NPA-I and with the WISC-R at NPA-II are described. For the given small sample size, only descriptive statistics are given for this group.

Last, IQ's of all patients ($N = 43$) were analysed at NPA-II by hierarchical regression analysis to investigate the largest possible group of patients and compare them with the siblings while controlling for age and test-shift (if a child was tested at NPA-I with WPPSI-R, and at NPA-II with the WISC-R).

For analyses 1 and 3, the results in patients and siblings are presented by: (a) descriptive results; (b) scatter plots; and (c) hierarchical regression analysis.

A comparison of the characteristics of patients and siblings showed that there were slight, insignificant differences between patients and siblings with respect to gender and age at testing; median age for siblings (Md = 8.2) was 1.8 years higher than that for patients (Md = 6.4).

The influence of gender as a possible confounding effect on the test scores was found nil. Finally, no strong regression assumption violations were found.[23]

Significance levels were established at $p < 0.05$.

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) WINDOWS 10.0 was used for the statistical analyses.

3. Results

3.1. Longitudinal analysis (analysis 1; subjects >6 years at NPA-I)

3.1.1. Descriptive results

Fig. 1 offers the results of 21 patients and 21 siblings who were assessed twice with the WISC-R. The mean scores of siblings and patients at NPA-I and NPA-II were high average compared to population norms.

Table 2 shows small differences over time if subtracting scores at NPA-I from NPA-II (Table 2). Hence, the positive differences indicate higher scores at NPA-II, and the negative differences indicate lower scores at the second assessment.

3.1.2. Scatter plots

Difference-scores for TIQ, VIQ and PIQ plotted against age mainly overlap in both groups (Fig. 2a–c). However, two young patients showed a decline of >10 IQ points at FS-IQ, versus none of the siblings (Fig. 2a). For VIQ, 3 patients and 3 siblings had a decline of >10 IQ points. Fig. 2b shows that particularly older patients and siblings scored positive. Three young patients and one older patient against none of the healthy siblings showed a decline of >10 IQ points at PIQ (Fig. 2c). Fig. 2a and c indicate that difference-scores for FS-IQ and PIQ are mainly positive, except for younger patients, who had slightly lower mean scores at NPA-II (Table 2). However,

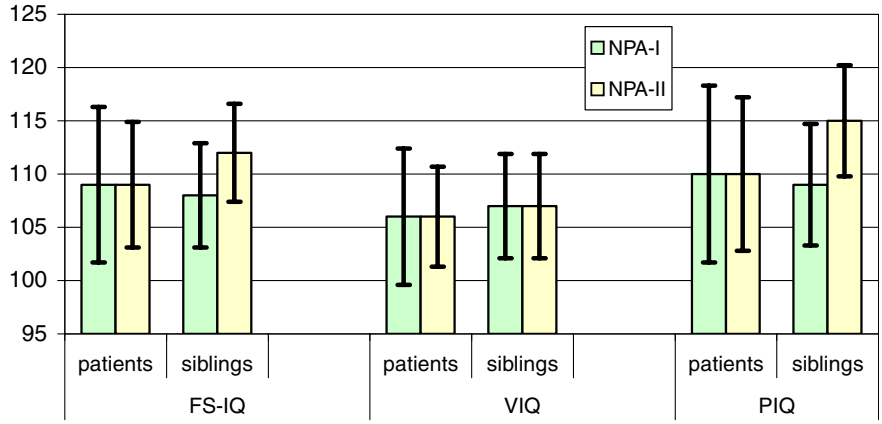

Fig. 1 – The descriptive bar graphs of WISC-R results of 21 patients and 21 siblings (>6 at NPA-I), at NPA-I and NPA-II with error bars indicating the 95% confidence interval.

Table 2 – The descriptive WISC-R difference-scores (NPA-II − NPA-I) in 21 patients and 21 siblings >6 at NPA-I (analysis 1)

	Patients (*N* = 21)				Siblings (*N* = 21)			
	Mean	SD	95% CI		Mean	SD	95% CI	
			Low	High			Low	High
Full-scale IQ (FS-IQ)	0.4	8.8	−3.6	4.4	4.3	6.5	1.3	7.2
Verbal IQ (VIQ)	0.5	10.8	−4.5	5.4	−0.5	7.9	−4.1	3.1
Performance IQ (PIQ)	0.0	9.0	−4.0	4.1	5.9	8.9	1.9	10.0

the number of young patients is small and there are even less number of young siblings; therefore, the possible age effect cannot be precluded.

3.1.3. *Hierarchical regression analysis*

Additionally, hierarchical regression analysis was conducted to compare the difference-scores for patients and siblings to detect the changes over time (Table 3). In the first step of hierarchical analysis, the age was included to control for a possible confounding effect and in the second step, the group factor was added to determine if this would lead to a meaningful change in the amount of explained variance (ΔR^2). In the third step, the interaction between age and group factor was included.

Table 3 shows that the age factor explains 10% of the variance of changes in FS-IQ and 5% in VIQ and PIQ; thus, age is probably a significant predictor of changes in FS-IQ ($\Delta R^2 = 0.100$; $p = 0.041$) if doing the WISC-R for the second time. Adding group as an explanatory variable to model does not lead to an important change in the amount of explained variance. So, there are no indications that the patients scored significantly lower than siblings. The results of hierarchical regression analysis do not demonstrate an interaction between age and group.

3.2. *Longitudinal analysis (analysis 2; subjects <6 years at NPA-I)*

The data of a subgroup of children who were <6 years and who had been tested with the WPPSI at NPA-I and with the WISC-R at NPA-II were analysed, to investigate the possible group × age interaction effect as mentioned before. Given the small sample size, only descriptive statistics will be given of this group.

Table 4 presents mean IQ-scores for patients and siblings at NPA-I (WPPSI-R) and NPA-II (WISC-R).

The performances of both patients and siblings remained average over time. However, the tests results of WPPSI-R and WISC-R cannot be compared, which will be discussed later.

3.3. *Cross-sectional, post-treatment analysis (analysis 3; all ages)*

3.3.1. *Descriptive results*

Table 5 offers WISC-R results (FS-IQ, VIQ, PIQ) of patients and siblings after cessation of treatment. IQs are high average for both groups on the WISC-R in comparison to population norms.

3.3.2. *Scatter-plots*

The scatter plots with IQ's for patients and siblings plotted against age indicate that scores in both groups mainly overlap (Fig. 3). As shown in Fig. 3, 3 patients have a FS-IQ < 90, whereas none of the siblings scored <90 (Fig. 3a). For VIQ, 2 patients and none of the healthy siblings scored <90 (Fig. 3b). For PIQ, 6 younger patients (younger than 8 years at diagnosis) and 1 older patient (older than 8 years at diagnosis) against none of the healthy siblings scored <90 (Fig. 3c). These findings support a group × age interaction effect for

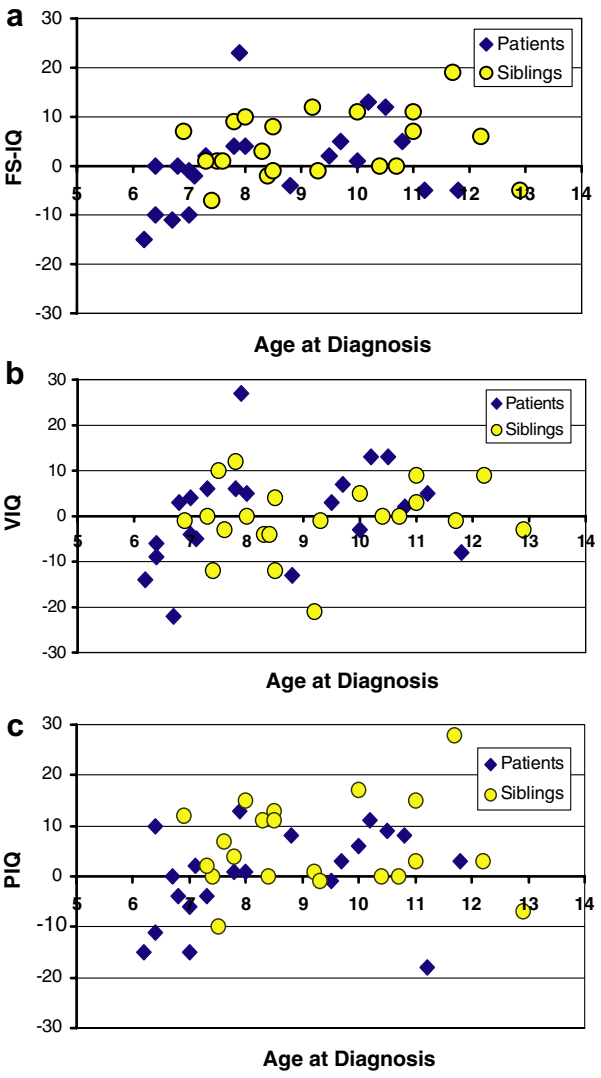

Fig. 2 – (a–c) Scatter plots of WISC-R difference scores (NPA-II – NPA-I) in 21 patients and 21 siblings >6 at NPA-I (analysis 1).

PIQ, indicating that younger patients have poorer performance. But again, this applies to a small number of patients.

3.3.3. *Hierarchical regression analysis*

Hierarchical regression analysis was conducted to compare the performances of patients with the siblings on WISC-R (Table 6). In the first step of the hierarchical analysis, age was included as a control variable. In the second step, test-shift was added to the regression analysis to find out if this factor leads to a meaningful change in the amount of explained variance (ΔR^2), which will be discussed later. In the third step, the group factor was added. In the fourth step, the interaction between age and the group factor was included. As Table 6 shows, the factor age explained a low amount of variance, except for PIQ in which age explains a moderate but significant amount of variance ($\Delta R^2 = 0.142$; $p = 0.001$). By adding group, no significant effects were found; thus, no indications were found that the patients scored lower than the siblings. For VIQ, a significant group × age interaction effect was detected ($\Delta R^2 = 0.056$; $p = 0.049$), with the younger patients scoring higher than the older patients and all siblings. For PIQ and FS-IQ, no significant effects were found.

4. Discussion

The purpose of the present study was to investigate the effects of chemotherapy-only on intelligence by means of the most optimal study design and sophisticated statistical procedures. The highlights of our study include a prospective design with a sibling control-group, strict methodology, little loss of patients during follow-up, a homogeneous patient group and a single neuropsychologist who did all the assessments.

The main conclusion of the longitudinal and post-treatment analysis is that there are no differences between patients and siblings. Moreover, both groups scored high average at both assessments compared to the population norms. This could be a result of the Flynn effect, accounting for an IQ rise of about 6 points since the test norms were

Table 3 – A comparison of WISC-R difference-scores (NPA-II – NPA-I) in 21 patients and 21 siblings (>6 at NPA-I) by hierarchical regression (analysis 1)

Model	df change		Full scale-IQ (FS-IQ)		Verbal IQ (VIQ)		Performance IQ (PIQ)	
			ΔR^2	*p*-Value	ΔR^2	*p*-Value	ΔR^2	*p*-Value
Age	1	40	0.100	0.041	0.051	0.152	0.054	0.137
Age, group	1	39	0.032	0.235	0.012	0.486	0.073	0.079
Age, group, interaction age and group	1	38	0.014	0.438	0.010	0.516	0.016	0.410

Table 4 – The mean scores of patients and siblings (<6 at NPA-1) at NPA-I (WPPSI-R) and NPA-II (WISC-R) (analysis 2)

	Patients (N = 11)				Siblings (N = 6)			
	Mean NPA-I (WPPSI-R)	SD	Mean NPA-II (WISC-R)	SD	Mean NPA-I (WPPSI-R)	SD	Mean NPA-II (WISC-R)	SD
Full scale-IQ (FS-IQ)	113.2	16.6	110.1	8.9	101.5	7.3	105.2	9.1
Verbal-IQ (VIQ)	115.6	15.5	115.5	9.9	99.5	8.4	103.5	8.4
Performance-IQ (PIQ)	107.1	13.1	101.7	10.8	106.0	19.6	105.7	11.7

Table 5 – The cross-sectional results of WISC-R at NPA-II in 43 patients and 27 siblings (all ages) after the cessation of therapy (analysis 3)

	Patients (N = 43)				Siblings (N= 27)			
	Mean	SD	95% CI		Mean	SD	95% CI	
			Low	High			Low	High
Full-scale IQ (FS-IQ)	107.4	12.5	103.6	111.3	110.4	10.5	106.3	114.6
Verbal IQ (VIQ)	108.1	11.5	104.6	111.7	106.0	10.5	101.8	110.1
Performance IQ (PIQ)	104.8	14.8	100.3	109.4	113.0	12.3	108.1	117.9

WISC-R; VIQ (information, similarities, arithmetic, vocabulary, digit span), PIQ (picture completion, block design, object assembly, coding, mazes); (CI = confidence interval).

collected in the early 80s.[24] If evaluated with more recent norms, these children would probably have average results.

As shown by the more extended hierarchical regression analysis and scatter-plots, the patients >8 years at diagnosis did not decline on intelligence over time. It seems that the group of younger patients (<8 years at diagnosis) might slightly decline on PIQ compared to older patients and the group of healthy siblings although not significant.

Our results agree with the longitudinal studies of Kingma and colleagues, Copeland and colleagues and Brown and colleagues who found no major differences between patients and controls on intelligence tests.[11,13,25] However, recent findings of the retrospective study by Montour-Proulx and colleagues showed a significant decline in PIQ.[26] Different outcomes can be explained by variability in interval and frequency of assessments, and the lack of a control group. Moreover, their patient group was younger than our group, but results of their's and our study are not contradictory when considering the youngest age groups.

There are two possible explanations for specifically young patients showing a relative decline in PIQ compared to siblings. The first explanation is that both the older patients and the siblings profit more from earlier testing than younger children.[27] Theoretically, the practise effect could be stronger for older children than for the younger children. Secondly, younger patients might score lower on PIQ at follow-up than their siblings as a true consequence of the higher susceptibility for the negative effects of chemotherapy in the immature brain.[28] Lastly, a general explanation for the differences between the younger and older patients in our study could be sample fluctuation, with no relation to treatment effect. The true meaning of a possible difference between the young and old patients cannot fully be established because of a relative lack of young siblings in the present study. Given the peak incidence of ALL (3–5 years), minimum age for the Wechsler scales (4 years) and the fact that the average number of children in Dutch families is <2, this problem cannot be solved. To establish a larger study population it would be interesting to run a multi-national study, however, differences in test versions (languages) and treatment protocols among countries would make comparisons difficult.

A few other remarks on methodology have to be made. First, the number of patients who refused to participate at NPA-I, and hence for the longitudinal comparison, could possibly yield bias in these study results. However, included patients did not differ in respect to age, sex, and disease characteristics from missing patients. Moreover, our percentage of missing patients is generally accepted for this kind of research.[29] Another group of patients was never referred,

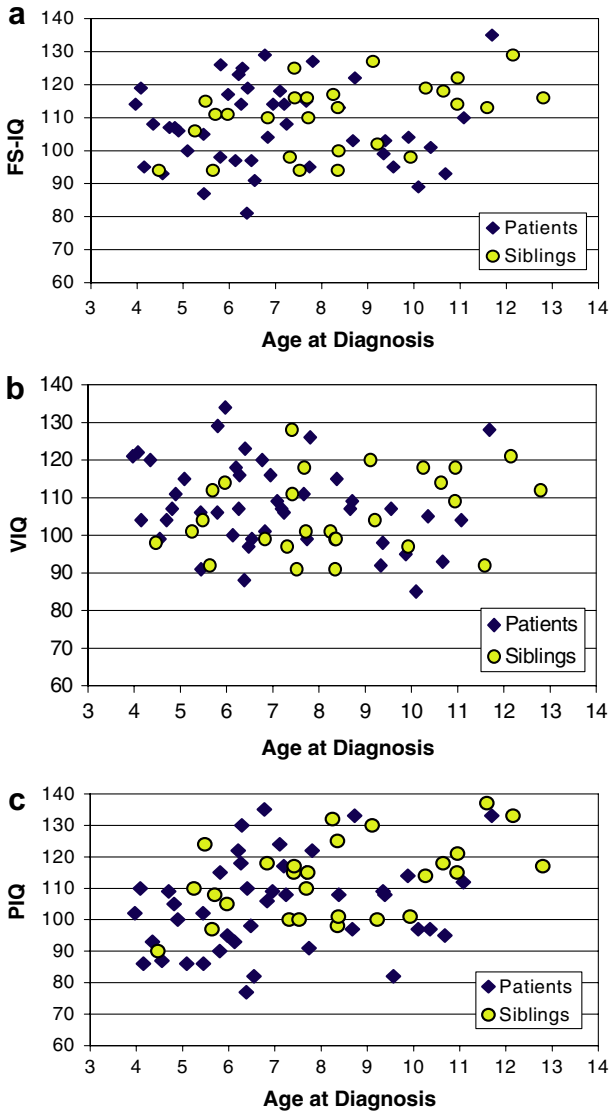

Fig. 3 – (a–c) The cross-sectional scatter plots of WISC-R at NPA-II in 43 patients and 27 siblings (all ages) after the cessation of therapy (analysis 3).

Table 6 – The cross-sectional comparison of WISC-R results at NPA-II of 43 patients to 27 siblings (all ages) by hierarchical regression analysis after the cessation of therapy (analysis 3)

Model	df change		Full scale-IQ (FS-IQ)		Verbal IQ (VIQ)		Performance IQ (PIQ)	
			ΔR^2	p-Value	ΔR^2	p-Value	ΔR^2	p-Value
Age	1	68	0.038	0.106	0.005	0.545	0.142	0.001
Age, test-shift	1	67	0.001	0.789	0.021	0.228	0.004	0.559
Age, test-shift, group	1	66	0.005	0.576	0.009	0.433	0.034	0.102
Age, test-shift, group, interaction age and group	1	65	0.031	0.144	0.056	0.049	0.007	0.473

unrelated to patients' or parents' characteristics. Second, a number of patients ($N = 11$) could not complete the full intelligence test at NPA-I and these patients might have profited less of earlier testing at the second assessment. To preclude any bias, we excluded these cases for the longitudinal analyses. Last, inevitable test-shift from the WPPSI-R to the WISC-R, as a consequence of the limited age range of intelligence tests, may have influenced the outcome for the younger group. Tests scores of WPPSI-R and WISC-R cannot be compared, given the different statistical properties and norm-scores. Bos and De Sonneville found a difference of approximately 7.5 IQ points between the older versions of WPPSI and WISC but their findings could not be used in our study.[30]

In summary, children with ALL treated with chemotherapy-only have normal intellectual functioning after cessation of two-year' intensive chemotherapeutic treatment including systemic and intrathecal MTX. Our findings also suggest that most children do not decline intellectually but it cannot be precluded that a few individual cases might deteriorate on PIQ. Further research must reveal whether the subtle differences found in young patients are temporary or will persist or even increase either by global damage or selective impairment to the brain. In clinical practice, it is important to monitor those individual patients who suffer from intellectual impairment to further improve their quality of life and to develop support programs. For future research it remains a challenge to elucidate the phenomenon of chemotherapy-induced impairment in some individual patients who might have a higher sensibility for negative sequelae.

Conflict of interest statement

None declared.

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