

# Comparison of intelligence quotient in children surviving leukemia who received different prophylactic central nervous system treatments

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## Abstract

**Background:** Neurocognitive deficits and decrease in intelligence quotient (IQ) is one of the complication of prophylactic central nervous system (CNS) treatment in acute lymphoblastic leukemia (ALL) patients. In this study, we compare the IQ in survivors of ALL that were treated with different prophylactic CNS treatments.

**Materials and Methods:** We compared 43 long-term survivors of ALL: 21 survivors with intrathecal methotrexate (IT MTX) as CNS prophylaxis, 22 with IT MTX+ 1800-2400 rads cranial irradiation and 20 healthy controls. The IQ was measured using the Raven's test in these patients.

**Results:** Raven's test revealed significant differences in IQ between the survivors of ALL that were treated with IT MTX, IT MTX plus cranial irradiation and control group. There was no significant difference in the IQ with respect to sex, age and irradiation dose.

**Conclusion:** We can that reveal that CNS prophylaxis treatment, especially the combined treatment, is associated with IQ score decline in ALL survivors. Therefore, a baseline and an annual assessment of their educational progress are suggested.

**Key Words:** Acute lymphoblastic leukemia, chemotherapy, intelligence quotient, radiotherapy

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## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cause of malignancy in children.<sup>[1]</sup> The average life expectancy of patients in 1950 was approximately 3 months.<sup>[2]</sup> With the advent of systemic chemotherapy, the remission rate increased from

less than 5% to 90%, but a substantial number of the patients sustained relapse at central nervous system (CNS) after their remission.<sup>[2]</sup> Prophylactic CNS treatment includes intrathecal methotrexate (IT MTX) alone or in combination with cranial irradiation (1800-2400 rads), which can prevent CNS relapse, increasing the 5-year survival rate of patients to more than 80%, but is not without disadvantages.<sup>[2,3]</sup>

Radiation, vincristine, prednisolone, methotrexate and high-dose cytarabine are medications that might have adverse effects on cognitive function.<sup>[4,5]</sup> Neurocognitive deficits usually become evident 1-2 years after radiation, and are progressive. The patients have difficulties in reading, languages and mathematics and younger age in intelligence quotient (IQ).<sup>[5]</sup>

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The exact pathogenesis of CNS damage is not clear. Cranial irradiation and IT MTX can both cause significant microangiopathy, demyelination and cerebral necrosis.<sup>[2]</sup>

Imaging findings show that white matter tracts and right frontal white matter loss may be the cause of cognitive difficulties observed in survivors,<sup>[1,6]</sup> and Mulhern *et al.* have shown an association between volume of white matter loss and full-scale IQ.<sup>[7,8]</sup>

Young age at the time of treatment, treatment with irradiation and chemotherapy, increasing radiation dose and female gender are risk factors for neurocognitive sequelae.<sup>[9]</sup>

Many studies have been conducted to assess these effects but, unfortunately, the results are not clear-cut. Some studies found intellectual deficit and others did not, and those that found deficits are not consistent with each other.

In this study, we compared the IQ in survivors of ALL that were treated with different prophylactic CNS treatments: IT MTX alone and IT MTX plus cranial irradiation.

## MATERIALS AND METHODS

This study was carried out at the Al-Zahra Hospital of Isfahan (central area of Iran) from May 2010 to February 2011.

All survivors of ALL who were between 5 and 15 years of age and at least 6 months past from the end of treatment were recruited to participate in this study. They were informed of the study by phone. None of the children enrolled in this study had a mental delay and chronic disease predating the diagnosis of leukemia and none of the survivors had a history of recurrence and bone marrow transplant. Specific treatment protocols varied, but all survivors received CNS prophylaxis with IT chemotherapy (MTX) or IT chemotherapy combined with cranial radiation (1800-2400 rads). Mental retardation, neurologic disorder and traumatic brain injury associated with alteration of consciousness were exclusionary criteria. Potential healthy siblings of participating survivors of ALL were recruited as the control group.

This study was approved by the institutional review board committee and informed consent was obtained from the parents.

A total of 43 ALL survivors [21 survivors with IT MTX as CNS prophylaxis (group1), 22 with IT MTX+1800-

2400 rads cranial radiation (group2) and 20 healthy controls (group3)] were enrolled in the study, and all of them completed the study.

Mean of age $\pm$ SD of the three groups in order was 9 $\pm$ 2.6 years in group 1, 12.2 $\pm$ 4.2 years in group 2 and 8.6 $\pm$ 3.1 years in the healthy control group ( $P=0.002$ ). The male/female ratio was 1.5, 1.9 and 2.3, respectively ( $P=0.8$ ).

The mean age at diagnosis of ALL was 4.4 years (SD=2.6, range=1.5-13 years) in group1 and 6.8 years (SD=3.7, range=2.9-13.3 years) in group 2 ( $P=0.8$ ). The mean time since end of treatment was 22 months (SD=15.2, range=6-58 months) in group 1 and 18 months (SD=15, range 6-60 months) in group2. Survivors of group 1 were given 14-16-times IT MTX and group 2 14-18-times IT MTX, and cranial radiation was given at 1800 rads in 13 patients (59%) and 2400 rads in nine patients (41%).

IQ was measured using Raven's test, which is a non-verbal IQ test and it does not rely on language to determine cognitive abilities. This test included multiple choice questions of abstract understandings. It allowed children to show pattern-recognition, attention to details, memory and spatial reasoning. This test is close to the functioning scales on a WISC-III (Wechsler Intelligence Scale-3<sup>rd</sup> Edition).

Raven's test is very easy to use and the cost is low. It has the highest predictive validity and with SD=16, IQ<76 is very low, 76-90 is low, 90-110 is normal, 110-132 is high and >132 is the Mensa level.<sup>[10-12]</sup>

Data obtained were analyzed through SPSS<sup>18</sup> software using the ANOVA test.

## RESULTS

There were significant differences in IQ between the survivors of ALL that were treated with IT MTX (group1), IT MTX plus cranial radiation (group2) and control group (group3). The mean $\pm$ SD was 101.3 $\pm$ 13.8, 94.8 $\pm$ 14, 105 $\pm$ 9.4, respectively, in group 1, group 2 and group 3;  $P=0.027$  [Figure 1].

The LFD (least significant difference) test revealed significant differences in IQ between the group 2 survivors and the control group ( $P=0.008$ ), but there was no significant difference between the ALL survivors who received IT MTX alone in comparison with the two other groups ( $P=0.11$  and  $P=0.26$ , respectively).

There was no significant difference in IQ with respect to sex (mean $\pm$ SD: Female=101 $\pm$ 13.3, male=100.4 $\pm$ 13.3;  $P=0.89$ ).

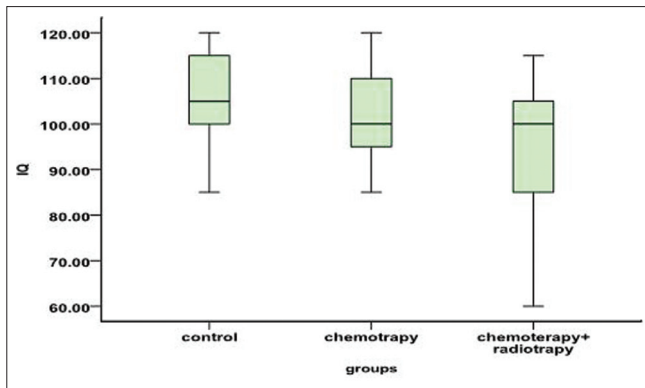


Figure 1: Comparison of the intelligence quotient in three groups

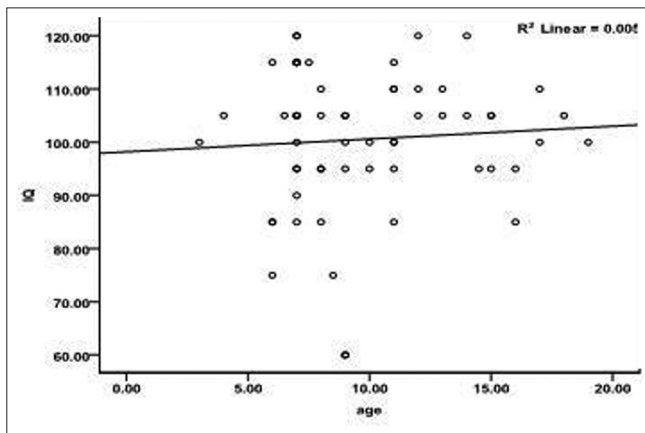


Figure 2: Correlation between the age at diagnosis and intelligence quotient scores

The Pearson correlation test revealed a weak relationship (7%) between the age at diagnosis and IQ scores, and this relationship was not significant,  $P=0.6$  [Figure 2].

There was no difference between IQ scores and irradiation dose between group 1 and group 2 ( $97.1\pm 10.1$  and  $92.3\pm 16.3$ , respectively).

## DISCUSSION

Consistent with some previous researches,<sup>[2,4,13-17]</sup> the results of this study indicate adverse effects of prophylactic CNS treatment, especially irradiation, on intelligence.

The first study about the effects of CNS irradiation on neuropsychologic functioning of children with ALL was done in 1975,<sup>[17]</sup> and then many studies were done about the effects of different forms of CNS prophylaxis on neuropsychological function, especially IQ of children with ALL.<sup>[2,13-17,18-21]</sup>

Most studies performed on leukemic children who received only IT MTX prophylaxis showed mild

intellectual deficit with mean IQ scores in the average range,<sup>[2,21-24]</sup> but other studies such as the study by Proulx *et al.*<sup>[4]</sup> reported significant adverse effects of cumulative dosage of IT MTX on performance IQ in 24 children (13 boys, 11 girls) that received IT MTX ( $17\pm 2-4$  times) without cranial irradiation (42-45% of the IQs for this group fell  $>1SD$  below the normative mean) and the study by Raymond-Spenden *et al.*<sup>[15]</sup> on survivors of ALL treated with CNS chemotherapy ( $n=21$ ), CNS chemotherapy plus 1800 rads cranial irradiation ( $n=20$ ) and healthy children ( $n=21$ ) showed “CNS chemotherapy, with and without cranial irradiation was associated with significantly lower levels of intellectual and academic functioning”.

Our study showed that the mean IQ scores of long-term survivors of ALL that were treated with IT MTX was lower than their healthy siblings. Although this decrease is subtle, it is consistent with the previous reports and shows the toxic effects of CNS chemotherapy.

Although the addition of cranial irradiation, especially 2400 rads, to CNS prophylaxis treatment in childhood ALL has been very effective in the reduction of CNS relapse from 75% to 80% to less than 10%, is associated with structural abnormalities and white matter changes and, finally, long-term difficulties in cognitive and academic functions.<sup>[1,14]</sup>

The oldest studies by Ivnik *et al.*, Meadows *et al.* (1981), Pfefferbaum-Levine *et al.* and Rowand *et al.* (1984) indicated IQ differences between irradiated and non-irradiated patients. Mulhern *et al.* (1991), in a prospective comparison of neuropsychologic performance of children surviving leukemia who received IT MTX plus 1800 rads cranial irradiation ( $n=23$ ) and 2400 rads ( $n=23$ ) or no cranial irradiation ( $n=26$ ) showed that 22-30% of the children exhibited a clinically significant deterioration greater than or equal to 15 points in uncorrected IQ value.<sup>[18]</sup>

Cetingul *et al.* (1999) also compared 19 children (15 male, four female) with ALL who were all given cranial irradiation (12-18 Gy,  $n=15$ , 73.6%) or (24 Gy,  $n=4$ , 21.1%) with 17 healthy siblings as the control group, and showed significantly low performance and total IQ scores;  $P=0.007$  and  $P=0.02$ .<sup>[14]</sup>

Our results are consistent with these findings, and irradiated patients had lower mean IQ scores in comparison with the control group ( $P=0.008$ ).

The mean age of diagnosis for ALL is 5 years, and age lower than 5 years is a risk factor for the neurotoxic

effects of CNS prophylaxis.<sup>[5]</sup> Brain myelination in children occurs in an inferior-to-superior and posterior-to-anterior fashion, and continues through adolescence.<sup>[1]</sup> For these reasons, any toxic agent as chemotherapy drugs and irradiation, especially in early age, may disrupt development of the white matter and cause regional white matter volume reduction, and these abnormalities are associated with impairment in cognitive functions.<sup>[1,23]</sup>

In the current study, there was a weak relationship between the age of diagnosis and IQ scores, which was in accordance with the findings of Cetingul, Mulhern and Kolotas,<sup>[14,18,20]</sup> and show the role of other factors except age.

One of the other risk factors is female gender, and the sensitivity of girls to neurotoxic effect of chemotherapy and irradiation is due to delay in brain maturation in this gender.<sup>[23]</sup>

In this study, there was no significant difference between sex and IQ scores probably due to the greater number of males in comparison with females.

Irradiation dose has been reported as another risk factor for neurotoxic sequelae of CNS treatment in ALL patients,<sup>[9]</sup> but Kolotas reported that irradiation does not predict a decrease in IQ, and the only predictor is time lapse between irradiation and IQ measurement.<sup>[20]</sup> Mulhern also did not show any significant decline in IQ in 23 survivors who received 2400 rads versus 23 patients who were treated with 1800 rads irradiation.<sup>[18]</sup> Against these studies, Halberg and Cetingul revealed the neurotoxic effect of 2400 rads irradiation versus 1800 rads on IQ scores of ALL survivors.<sup>[13,14]</sup>

In our study no significant differences were observed between the two radiation groups and larger samples are recommended for further research in this area.

Although this study was limited by small size. But, despite this limitation, the results revealed neurotoxic effect of CNS treatment on IQ scores survivors of ALL.

## CONCLUSION

We can reveal that CNS prophylaxis treatment, especially combined treatment, is associated with a decline in IQ scores in ALL survivors. Therefore, a baseline and an annual assessment of their educational progress should be monitored and, if needed, use special educational services.

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