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# Quantitative Assessment of Cerebral Atrophy During and After Treatment in Children with Acute Lymphoblastic Leukemia

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**RATIONALE AND OBJECTIVES. The authors evaluate quantitatively brain atrophy induced by central nervous system prophylaxis in children treated for acute lymphoblastic leukemia during and after therapy completion.**

**METHODS. Measurements of the width of the subarachnoid compartments were performed in 243 brain computed tomography (CT) examinations of 196 children examined during (125) and/or after (71) treatment for acute lymphoblastic leukemia without central nervous system involvement. Data were compared with normative data.**

**RESULTS. Diffuse brain atrophy was observed in 74% and 65% of the CT examinations performed during and after cessation of treatment, respectively. The highest incidence of brain atrophy (78%) occurred during the administration of intrathecal chemotherapy. All children younger than 2 years of age exhibited brain atrophy.**

**CONCLUSIONS. Brain atrophy is the principal CT finding in the majority of children treated for acute lymphoblastic leukemia and it can be attributed mainly to intrathecal chemotherapy. This finding can be observed long after therapy completion.**

**KEY WORDS. Acute lymphoblastic leukemia; brain, infants and children; subarachnoid space; chemotherapy; computed tomography.**

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CENTRAL NERVOUS SYSTEM (CNS) prophylaxis with intrathecal chemotherapy and cranial irradiation in children with acute lymphoblastic leukemia (ALL) may cause brain damage that is depicted on neuroimaging studies.[1–3] Computed tomography (CT) findings include cerebral calcifications, white-matter low-density areas, or enlargement of the subarachnoid spaces.[1–6] In previous studies, cerebral atrophy has been considered the most frequent CT finding occurring either in 8% to 12%,[1] 25% to 28%,[2] 30%,[3] or 43%[4] of the children with ALL. In some series, ventricular dilatation has been observed more often than enlargement of the cortical sulci,[1,3] whereas in others[5,6] brain atrophy has been considered of cortical type. Although some authors have suggested that cerebral atrophy is a reversible consequence of steroids,[7] others have anticipated that it is a permanent sequel of CNS prophylaxis with intrathecal chemotherapy and of cranial irradiation.[3,4]

In the current study, brain atrophy related to antileukemic therapy was studied systematically on CT. The size of the various subarachnoid compartments was assessed quantitatively in an attempt to examine the type, incidence, and potential reversibility of brain atrophy, as well as to investigate any probable association between brain atrophy and specific components of therapy in brain CT examinations of children treated for ALL. A detailed, objective, and reproducible assessment of cerebral atrophy may be of value in assessing the side effects of different types of antileukemic therapy or in associating neuropsychologic sequelae with morphologic alterations in the brain of children with ALL.

## Materials and Methods

The study included all children with ALL referred for brain CT in our departments during a 4-year period (Octo-

ber 1991 to October 1995) that satisfied the following criteria: children with newly diagnosed leukemia without CNS involvement or typical symptoms of CNS toxicity due to chemotherapy, examined during treatment (group A), and children with ALL examined after the cessation of treatment (group B), in complete remission of their disease without evidence of CNS involvement at diagnosis or history of ALL relapse. Children with ALL without CNS involvement or CNS complications as well as children in complete remission of their disease do not routinely undergo brain CT in our hospitals. Thus, a total number of 243 brain CT examinations of 196 children referred by the clinicians were selected; 95 patients had one CT and 101 had two CT examinations. None of the patients had CT findings indicative of CNS malformation, increased intracranial pressure, or space occupying lesion in the brain or the cerebellum.

Group A included 140 brain CT examinations of 125 children (76 boys, 49 girls, ages 8 months to 14 years old); 110 had one brain CT and 15 had two brain CT examinations during treatment. For the purposes of the current study, antileukemic therapy was considered to be divided into two specific time periods separated by a time interval during which cranial irradiation was administered. Before cranial irradiation, CNS prophylaxis was administered (6–9 doses of methotrexate administered intrathecally) in parallel with induction remission and consolidation therapy. Depending on the clinical and laboratory data, combinations of the following antileukemic agents were given by mouth or intravenously for induction remission and consolidation therapy: vincristine, prednisone, farmorubicin, and L-asparaginase with or without cyclophosphamide for induction remission therapy; and methotrexate, cytocine-arabinoside, prednisone with or without 6-mercaptopurine, vincristine, L-asparaginase, dexamethasone, 6-thioguanine, vindesine, ifosfamide, and daunomycin for consolidation therapy. During CNS prophylaxis with intrathecally given methotrexate (lasting 4–6 months), 54 CT examinations were performed on 52 children (30 boys, 22 girls; subgroup $A_1$). Intrathecal chemotherapy was followed by cranial irradiation with 1800 cGy in 12 to 15 doses. After cranial irradiation (ie, in the second period of antileukemic therapy during maintenance therapy), 86 CT examinations were performed on 73 (46 boys, 27 girls) children (subgroup $A_2$). Maintenance therapy was administered for 2 years with 6-mercaptopurine and methotrexate by mouth and reinductions of vincristine and prednisone. Thirty-two children of group A (11 of subgroup $A_1$ and 21 of subgroup $A_2$) were subjected to CT at diagnosis, before therapy onset. These brain CT examinations were used as baseline for the 32 children that underwent CT during treatment. Mean ages at diagnosis were 6.9 years for group A, 8.2 years for subgroup $A_1$, and 6 years for subgroup $A_2$. Twenty-nine children were younger than 2 years of age at diagnosis.

Group B consisted of 71 CT examinations of 71 children (46 boys, 25 girls) 4 to 16 years old (mean 9.7 years), that underwent CT 2 months to 8 years (mean 2.8) after treatment completion. They had been cured with various treatment protocols, including intrathecal and intravenous chemotherapy and cranial irradiation; 27 of them had a CT during treatment.

The clinical data of each patient was noted and the CT examinations were stored in the optical disks of the CT units. After the end of the 4-year data-collection period, the stored images were reviewed and measurements were performed by the same author (PP) masked to the group, age, and gender of the patient by means of the CT software.

All brain CT examinations were performed with consecutive 5-mm sections, parallel to the canthomeatal line, in the posterior fossa and skull base and 10 mm in the rest of the cranium, except for young infants where 5-mm scans were used. The same examination protocol has been used previously in the determination of normative data for the cerebrospinal fluid (CSF) compartments.[8,9] Children younger than 5 years were sedated, when necessary, with 80 to 100 mg/kg of chloral hydrate. The size of the cerebrospinal fluid spaces was assessed by the following measurements:

1. The minimum width of the bodies of the lateral ventricles;
2. The maximum distance between the anterior horns of the lateral ventricles;
3. The distance between the caudate nuclei;
4. The width of the third and
5. Fourth ventricles;
6. The anteroposterior and transverse diameters of the basal cistern, which were added;
7. The maximum width of the Sylvian and
8. Interhemispheric fissures;
9. The maximum width of the peripheral CSF space, either at the frontal, temporal, parietal, or occipital regions; and
10. The maximum width of the cortical sulci.

Measurements of the ventricles and the basal cistern were divided by the sum of the maximal longitudinal and transverse diameters of the skull (measurements 1–4, 6) or the posterior fossa (measurement 5) to form six ratios (CSF indices) that referred the extent of the CSF compartments to the cranial size.[8] The CSF indices were compared with the corresponding age-matched normative data (normal range: mean value $\pm$ 2 standard deviations), obtained from a previous study on 247 normal brain CT examinations.[8] It has to be noted that normal values of the CSF indices do not differ between boys and girls and

TABLE 1. Measurements of the Extent of Cerbrospinal Fluid Spaces in Children Undergoing Chemotherapy for Acute Lymphoblastic Leukemia

| | Subgroup $A_1$* (54 CT examinations) | Subgroup $A_2$* (86 CT examinations) | Group B* (71 CT examinations) |
|---|---|---|---|
| Indices | | | |
| LV | 0.132 ± 0.048 | 0.129 ± 0.036 | 0.118 ± 0.039 |
| AH | 0.128 ± 0.036 | 0.121 ± 0.035 | 0.115 ± 0.040 |
| BN | 0.051 ± 0.017 | 0.048 ± 0.013 | 0.042 ± 0.010 |
| TV | 0.022 ± 0.010 | 0.020 ± 0.009 | 0.017 ± 0.007 |
| FV | 0.107 ± 0.029 | 0.107 ± 0.021 | 0.102 ± 0.026 |
| BC | 0.181 ± 0.036 | 0.169 ± 0.042 | 0.168 ± 0.043 |
| Measurements (mm) | | | |
| SF | 4.8 ± 2.8 | 4.5 ± 2.1 | 4.1 ± 2.8 |
| IF | 5.1 ± 3.1 | 4.9 ± 2.2 | 4.5 ± 2.5 |
| PS | 4.4 ± 2.5 | 4.4 ± 2.8 | 4.6 ± 3.1 |
| CS | 2.3 ± 1.1 | 2.2 ± 1.2 | 1.9 ± 1.0 |

*Values are mean ± 2 standard deviation.

Subgroup $A_1$: children examined during administration of intrathecal chemotherapy, prior to cranial irradiation; Subgroup $A_2$: children examined after CNS prophylaxis during maintenance therapy; Group B: children examined after cessation of therapy; LV: lateral ventricles index; AH: anterior horns index; BN: bicaudate nuclei index; TV: third ventricle index; FV: fourth ventricle index; BC: basal cistern index; SF: sylvian fissures; IF: interhemispheric fissure; CS: cortical sulci; PS: maximum width of the cerebrospinal fluid space at the frontal, temporal, parietal, or occipital regions.

remain constant after the age of 2 years. Measurements 7 to 10 were considered abnormal if they exceeded the corresponding upper normal limits for the Sylvian fissure (3 mm), interhemispheric fissure (4 mm), peripheral CSF space (4 mm), and cortical sulci (2 mm), established in a previous study[9] on 96 normal brain CT examinations. The Student's *t* test was used to compare the size of the CSF compartments between the CT examinations of (a) boys and girls, (b) the 32 children of group A that had one CT before and one CT during treatment, (c) subgroups $A_1$ and $A_2$, (d) groups A and B, and (e) the 27 children in group B that had one CT during and one CT after the completion of treatment. Data distribution proximity to the normal distribution was assured[10] before applying the Student's *t* test. Data processing and statistical analysis were performed on a computer.

## Results

Measurements of the extent of the CSF spaces in subgroups $A_1$, $A_2$, and group B are presented in Table 1. In subgroup $A_1$, 30 (56%) children had all the CSF compartments enlarged, 12 (22%) had normal CSF spaces, and 12 (22%) had some of the subarachnoid spaces widened. In subgroup $A_2$, 35 (41%) children had all the CSF spaces widened (Fig. 1), 24 (28%) had normal subarachnoid spaces, and 27 (31%) had some of the CSF compartments enlarged. In group B, dilatation of all CSF spaces was found in 31 (44%) children, enlargement of some CSF compartments in 15 (21%), and in 25 (35%) all measurements were within the normal limits. In the 32 CT examinations performed before therapy onset, all CSF spaces were found to be normal. The CSF compartments did not differ in size between boys and girls ($P > 0.10$) in either groups $A_1$, $A_2$, or B. The size of each CSF compartment did not significantly differ ($P > 0.10$) between subgroups $A_1$ and $A_2$, although the mean values in $A_1$ were larger than the corresponding values in $A_2$ (Table 1).

All CSF compartments in group A were found to be larger than in group B; differences were statistically significant ($0.05 < P < 0.001$), except for the lateral ventricles and fourth ventricle indices, the peripheral CSF space, and the cortical sulci. In the 32 children of group A that had one CT before and one CT during treatment, the size of each CSF compartment during treatment was found larger than the corresponding one before therapy onset (Table 2); differences were significant ($0.05 < P < 0.01$), except for the cortical sulci and the fourth ventricle index. In the 27 children of group B that had one CT during and one CT after the completion of therapy, all the CSF spaces were larger during treatment (Table 2); however, only the anterior horns distance, the bicaudate nuclei distance, the third ventricle, and the basal cistern indices differed significantly ($P < 0.05$). A probable reason that some of the above mentioned differences did not reach a statistically significant level might be the number of patients involved and the variance of some of the normal measurements.

Widening of all the CSF spaces was found in 12 of the 14 children of group A that were younger than 2 years. In the remaining 2 children, only some of the CSF compartments were normal in size. Low density areas in the periventricular white matter were observed in 2 children of subgroup $A_2$ and cerebral calcifications were found in 1 child of group B.

## Discussion

Prognosis of children with ALL has improved significantly by the use of combinations of intensive intravenous

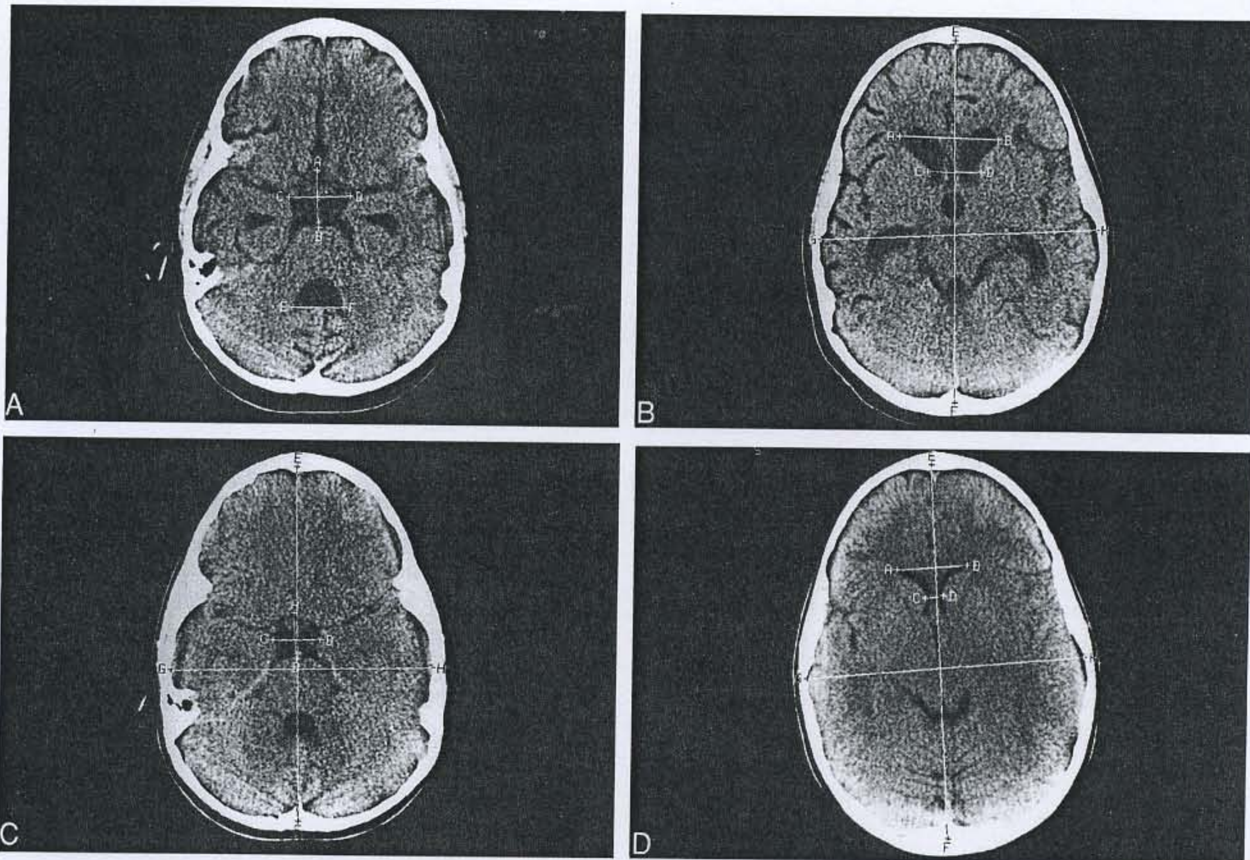

Figure 1. Computed tomography measurements of (A) the anteroposterior [AB] and transverse [CD] diameters of the basal cistern and the width of the fourth ventricle [EF], (B) the anterior horns [AB], and bicaudate nuclei distance [CD] in a 6-year-old boy with acute lymphoblastic leukemia, 18 months after the onset of therapy. (C) and (D) show corresponding reference measurements in the computed tomography examination of the same child performed before the onset of treatment.

chemotherapy and CNS prophylaxis during the last decades.[11] Because various therapeutic protocols provide equally efficient cure rates, reducing treatment toxicity without diminishing drug effectiveness is of primary importance.[3,11] The most frequent sequalae of CNS prophylaxis, appearing in approximately three quarters of patients, concern cognitive functions impairment that differs significantly among long-term ALL survivors.[12] There are several accurate tests to determine the degree of damage of neurocognitive functions in ALL survivors as well as an expanding published experience on this issue.[4,6,12] A detailed quantitative evaluation of brain atrophy, which is the most common neuroradiologic finding in children with ALL, could be of value in associating morphologic alterations with functional impairment.

According to the findings of the current study more than three fourths of the children with ALL that underwent CT during treatment had widened CSF spaces. Brain atrophy was of diffuse type with similar incidence of enlargement of the intra- and extraventricular CSF compartments. Therapy did not seem to have cumulative effects on cerebral atrophy; higher incidence of CSF spaces dilatation was observed in the early stages of the treatment during the administration of intrathecal chemotherapy, whereas children examined later, after cranial irradiation, exhibited lower incidence of cerebral atrophy. Therefore, intrathecal chemotherapy may be the main reason for cerebral atrophy and cranial irradiation with a dose of 1800 cGy seems to provide a smaller contribution to cerebral atrophy. There are only a few previous studies on neuroimaging findings in children with ALL examined during treatment, with conflicting views. Ochs et al[7] have found brain atrophy in 30% of 108 children during CNS prophylaxis by radiotherapy and intrathecal administration of chemotherapeutic agents and steroids. Atrophy was reverted to normal within 6 weeks after cessation of CNS prophylaxis while intravenous chemotherapy was being administered, and the authors concluded that brain atrophy was the result of steroids. However, CT examinations were performed on lower resolution old technology CT units and brain atrophy was evaluated using criteria obtained from CT examinations of adults. Duffner et al[13]

TABLE 2. Measurements of the Extent of Cerebrospinal Fluid Spaces in 32 Children with One Computed Tomography Before and One Computed Tomography During Treatment and in 27 Children with One Computed Tomography During and One Computed Tomography After Therapy Completion

| | 32 children* | | 27 children* | |
|---|---|---|---|---|
| | Before treatment | During treatment | During treatment | After treatment |
| Indices | | | | |
| LV | 0.102 ± 0.013 | 0.123 ± 0.034 | 0.127 ± 0.036 | 0.121 ± 0.039 |
| AH | 0.107 ± 0.011 | 0.126 ± 0.029 | 0.128 ± 0.033 | 0.113 ± 0.041 |
| BN | 0.029 ± 0.005 | 0.047 ± 0.010 | 0.048 ± 0.015 | 0.039 ± 0.010 |
| TV | 0.007 ± 0.009 | 0.020 ± 0.012 | 0.021 ± 0.007 | 0.015 ± 0.012 |
| FV | 0.075 ± 0.010 | 0.078 ± 0.026 | 0.104 ± 0.030 | 0.103 ± 0.029 |
| BC | 0.128 ± 0.015 | 0.172 ± 0.038 | 0.180 ± 0.041 | 0.166 ± 0.038 |
| Measurements (mm) | | | | |
| SF | 2.1 ± 0.18 | 4.4 ± 2.1 | 4.6 ± 2.9 | 4.3 ± 2.5 |
| IF | 2.6 ± 0.20 | 4.8 ± 1.9 | 5.0 ± 2.3 | 4.3 ± 2.4 |
| PS | 1.9 ± 0.15 | 4.7 ± 2.2 | 4.5 ± 2.9 | 4.2 ± 3.2 |
| CS | 1.0 ± 0.07 | 1.3 ± 1.8 | 2.1 ± 1.2 | 1.7 ± 1.1 |

Values are mean ± 2 standard deviation.

LV: lateral ventricles index; AH: anterior horns index; BN: bicaudate nuclei index; TV: third ventricle index; FV: fourth ventricle index; BC: basal cistern index; SF: sylvian fissures; IF: interhemispheric fissure; CS: cortical sulci; PS: maximum width of the CSF space at the frontal, temporal, parietal, or occipital regions.

have found ventricular dilatation in 17 of 22 children with ALL examined during treatment in a study that included only children with CNS leukemia. Asato et al[14] could not clearly observe dilatation of the cortical sulci or lateral ventricles in the magnetic resonance imaging examinations of 16 children treated for ALL.

A finding of particular interest in the current study was that all children younger than 2 years of age at diagnosis had dilated CSF compartments. This is in agreement with results of studies confirming that children treated at younger ages generally perform more poorly on measures of cognitive function.[12]

Neuroimaging findings in ALL survivors, examined months to years after completion of therapy, have been described in several studies.[1–4,6] However, it is difficult to draw definite conclusions from studies that comprised children with or without CNS involvement or ALL relapse, with different time intervals between therapy completion and CT examination, and cured with different protocols. Nevertheless, brain atrophy has been found to be the most frequent neuroimaging finding, but incidences varied from 8% to 43%[1–4] and brain atrophy has been considered central,[1,3] cortical,[4–6] or diffuse.[2] In the current study, diffuse enlargement of the intra- and extraventricular CSF compartments was observed in about two thirds of the children that were examined after the termination of chemotherapy and in complete remission of their disease. The incidence of brain atrophy found in the current study was much higher than what it previously has been reported. This could be attributed to different methods used in the evaluation of the subarachnoid space. In the current study a quantitative assessment was performed by measuring the extent of the CSF compartments, while in previous studies brain atrophy has been evaluated mainly by visual inspection using subjective criteria. Nevertheless, the high incidence of brain atrophy found here should not be surprising. In a study on late effects of CNS prophylaxis for ALL, nearly three fourths of children that had been treated 5 to 12 years before evaluation were found to have mild to severe learning problems.[12]

The difference in the incidence of brain atrophy among children under treatment and those being examined after the cessation of therapy, may be related to the hypothesis that cerebral atrophy is partly reversible. This could be attributed to steroids administered during treatment, because they temporarily can induce dilatation of the subarachnoid space. However, enlargement of the CSF spaces should be mostly due to CNS prophylaxis inducing cerebral atrophy that can be observed long after therapy completion.

In contrast to the findings of previous studies,[1–3,5–6] white-matter low-density areas or cerebral calcifications were rare findings in the current study. However, hypodense areas have been noted mainly in children with neurotoxic symptoms during treatment[15] or with CNS leukemia,[13] but our study did not include such patients. The presence of calcifications has been associated with the administration of radiotherapy.[5,16] The rarity of this finding in our study probably was due to the lower dose (1800 cGy) of cranial irradiation administered instead of the 2400 cGy used in previous studies.[1,5,6,11] As the frequency of calcifications and low-density areas in the white matter will diminish with newer, less toxic protocols for CNS prophylaxis, brain atrophy would be the only radiologic finding in most cases.

Previous authors have attempted to correlate cognitive

impairment with neuroimaging findings in ALL survivors but their results are conflicting; Brouwers et al[4,6] have found a rough correlation between neuroimaging abnormalities and neuropsychologic sequalae, but Kingma et al[17] have found no correlation. Additionally, CT findings have been used in comparing neurotoxicity of protocols for CNS prophylaxis.[3,16] Because brain atrophy is found in the majority of children with ALL, a detailed and reproducible quantitative assessment of the subarachnoid spaces would allow for grading of atrophy in the attempt to correlate morphologic alterations with treatment toxicity or sequalae.

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