GSA may enable us to evaluate hepatic functional reserve accurately and to predict whether liver function will improve or not. That there is almost complete overlap between acute and chronic hepatitis in the receptor index and index of blood clearance shows that hepatic functional reserve is similar in the two conditions. The smaller overlap between cirrhosis and FHF shows that some patients with cirrhosis have the same hepatic functional reserve as some patients with FHF.

In decision making about the indications for liver transplantation in FHF, early prediction of the outcome is important. Bernuau et al. (*16*) found the patient's age, serum factor V concentration and serum alpha-fetoprotein concentration to be useful in the prediction of the outcome of FHF. O'Grady et al. (*17*) found that the prognosis was poor when the etiology was non-A, non-B hepatitis or a drug reaction, when the patient's age was less than 11 yr or more than 40 yr, or when jaundice had been present for more than seven days before the onset of encephalopathy. These various factors are not direct indicators of functional reserve. In a study by Donaldson et al. (*18*), patients with FHF underwent transjugular liver biopsy. Necrosis of 70% or more of the area of a section prepared from the specimen was found in 2 of the 19 patients who survived but in 20 of the 35 patients who later died, so the results of histological examination were useful in the prediction of survival. However, this method is invasive and hemorrhage may result. Our method is noninvasive.

CONCLUSION

Hepatic receptor imaging with ^{99m}Tc-GSA could be used to evaluate the hepatic function reserve of various liver diseases noninvasively. This method should be useful clinically in the establishment of the diagnosis and prognosis for patients with FHF.

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Brain Perfusion after Treatment of Childhood Acute Lymphoblastic Leukemia

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Children with acute lymphoblastic leukemia (ALL) have impairment in their neuropsychological functioning and morphological changes in their brain after cranial irradiation and chemotherapy. The aim of this study was to identify possible brain perfusion defects caused by different types of treatment and their association with abnormalities in cerebral MRI and neuropsychological and clinical neurological findings. **Methods:** Twenty-five consecutive children with ALL at the cessation of chemotherapy or after 1 yr were included. All of the children were given intravenous and intrathecal methotrexate for central nervous system therapy, 13 of them received cranial radiation therapy. Brain SPECT, cerebral MRI, clinical neurological and neuropsychological evaluations were performed. **Results:** Eleven of the 25 patients (44%) had brain perfusion defects in SPECT, eight of whom were treated with chemotherapy alone, and three received cranial irradiation. Two patients had small bilateral white matter changes on MRI; their brain SPECT scans were abnormal, although the findings were not related. Impairment of neuropsychological functioning was found in 86% of the patients tested. No significant difference between the patients with abnormal and normal SPECT were found. Those patients with abnormal SPECT were younger than those with normal SPECT and had received more frequent intravenous methotrexate infusions. **Conclusion:** Brain SPECT detected perfusion defects that had occurred after treatment for childhood ALL. These defects may be related to frequent administration of a combination of intravenous and intrathecal methotrexate and/or young age.

Key Words: SPECT; brain perfusion; acute lymphoblastic leukemia; methotrexate neurotoxicity

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Along with the improved prognosis for childhood acute lymphoblastic leukemia (ALL), the importance of the late treatment-related sequelae has increased. Central nervous system treatment, typically consisting of intrathecal and intravenous methotrexate with or without cranial irradiation, is an

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essential component of the therapy but is found to result in adverse long-term neurological and neuropsychological effects. Intellectual functioning is impaired after cranial irradiation, especially in children under 5 yr of age (*1*), and this finding has resulted in discontinuation of the use of cranial irradiation in many protocols and reliance primarily on intrathecal and intravenous chemotherapy. Chemotherapy alone, however, has also proved to result in brain damage in the form of white matter changes on MRI scans (*2*), decreased glucose metabolism on PET scans (*3,4*), clinical neurological symptoms (*5*) and neuropsychological deficiencies (*6*). The mechanisms and incidence of these changes are still not completely understood. Vascular changes have also been proposed as one side effect, an opinion supported by occasional stroke-like episodes after methotrexate treatment (*7*), vascular changes in neuropathological examinations (*8*) and decreased brain perfusion after methotrexate infusion in an animal experiment (*9*).

The aim of this study was to use SPECT to detect possible brain perfusion abnormalities after treatment for childhood ALL and to compare these data with MRI results and neuropsychological and clinical neurological examinations. The results could contribute to our understanding of the mechanisms of treatment-related neurotoxicity as well as further the development of central nervous system treatment protocols.

MATERIALS AND METHODS

Patients

The series included 25 consecutive children (14 boys, 11 girls; age range 4.9–16.2 yr; mean age 9.3 yr) treated for ALL whose therapy was completed between April 1992 and August 1995. Patients were divided into three risk groups: standard risk (age range 2.7–7.8 yr, median 4.1 yr, at diagnosis), intermediate risk (age range 2.9–10.0 yr, median 3.6 yr, at diagnosis) and high risk (age range 2.8–13.5 yr, median 9.5 yr, at diagnosis) based on the criteria used in the Nordic countries. The main criteria were the initial leukocyte count and age at diagnosis, while the special high risk criteria were mediastinal infiltration, central nervous system involvement, T- or B-cell ALL and chromosomal translocations (*10*) (Table 1). Patients with trisomy 21 were excluded from this series.

The patients with newly diagnosed ALL had been treated according to the Nordic protocol, except for three patients in the intermediate risk group who had been treated according to the ALL-BFM-83 protocol (*11*). There were two patients with a relapse, one of whom (Patient 24) received the Nordic-90 high risk treatment and the other (Patient 25), with a second relapse, the ALL-BFM-83 high risk treatment.

Remission was induced and consolidated in all protocols with 7 wk of standard treatment with prednisolone, vincristine, doxorubicin and L-asparaginase. The central nervous system therapy consisted of intrathecal and intravenous methotrexate in all protocols. Radiation therapy was included in the ALL-BFM protocols and in the Nordic high risk protocol for patients over 5 yr of age. Continuation therapy, which lasts up to 2 or 2.5 yr from diagnosis, included per-oral mercaptopurine daily and per-oral methotrexate weekly, except in the Nordic high risk patients. Their continuation therapy was given according to a modified LSA2-L2 protocol (*12*), which includes cycles of nine drugs (thioguanine, cyclophosphamide, hydroxyurea, daunomycin, methotrexate perorally and intrathecally, carmustine, cytosine arabinoside and vincristine). All the protocols included prednisolone, but dexamethasone was included in only the intermediate and high risk protocols. The chemotherapy and cranial irradiation included in the protocols are shown in Figure 1.

TABLE 1
Criteria for Risk Groups of Children with ALL

High risk (HR)	WBC* > 50 × 10^9/l
	CNS leukemia
	Mediastinal mass
	T- or B-cell ALL
	Chromosomal translocation
Intermediate risk (IR)	No HR criteria
	Age 2- 10 yr and WBC 10–50 × 10^9/l or
	Age 1- 2 yr and WBC ≤ 50 × 10^9/l
Standard risk (SR)	No IR or HR criteria
	Age 2- 10 yr and WBC ≤ 10 × 10^9/l

*WBC = white blood cell count

The first four patients had brain SPECT imaging and clinical neurological examinations between 9–15 mo after cessation of their therapy; all the other examinations were performed during the last hospitalization (about 1 mo) before the cessation of per-oral continuation therapy. There were three patients on whom a neuropsychological examination could not be performed: one was receiving treatment for psychiatric problems, which had been present before the diagnosis of ALL; one (Patient 6) was bilingual, so that the results of the neuropsychological examination were not reliable; and one (Patient 7) suffered a central nervous system relapse before the neuropsychological examination, which had been delayed 1 mo, could be performed.

The investigation was performed according to the provisions of the Declaration of Helsinki and approved by the Ethical Committee of the Faculty of Medicine, University of Oulu. Oral informed consent was obtained from the parents and/or patients.

Brain SPECT

Brain SPECT was performed using either ^{99m}Tc-HMPAO for the first 12 patients or ^{99m}Tc-ECD, according to the patients' weight. To achieve an attenuated sensory state, the patient's eyes were covered with patches and the child was lying supine with the head secured to the bed in a darkened quiet room for 10 min before intravenous tracer injection. Their eyes were still covered during the injection and for about 5 min afterwards. SPECT was performed 15–60 min after intravenous tracer administration. The images were acquired with a single-head camera equipped with a slant-hole collimator before November 1994 or with a double-head rotating gamma camera equipped with a fanbeam collimator after that. Sixty-four projections in a 128 × 128 matrix acquired over a 360° circular orbit, radius about 14 cm, were obtained, and each view contained an average of 65/45 kcts (for the double- or single-head, respectively). The filtered backprojection algorithm used a Butterworth filter with a cutoff frequency of 0.22 and an order of 5.0. No attenuation correction was used because an ideal attenuation correction method that accounts for the real outlines of the skull was not available. Two orbito-meatal line-oriented transverse, sagittal and coronal sections, 9.4 mm thick, were processed. In addition to visual interpretation by an experienced nuclear medicine physician, two semiquantitative methods were used to compare the tracer distributions in the right and left hemispheres. In the first, a two pixel-wide strip was placed over the transversal slice (occasionally coronal), and a count profile curve was produced (Fig. 2). The counting rate over the pathological area was then compared with the symmetrical normal area of the other hemisphere. Secondly, hemispheric asymmetry was measured using irregular regions of interest (ROIs) located symmetrically over the right and left cortical areas. Asymmetry between the hemispheres was calculated in percentages as (=100 × (max − min)/max). The cutoff point for hemispheric asymmetry was ≥ 12%, as quoted in

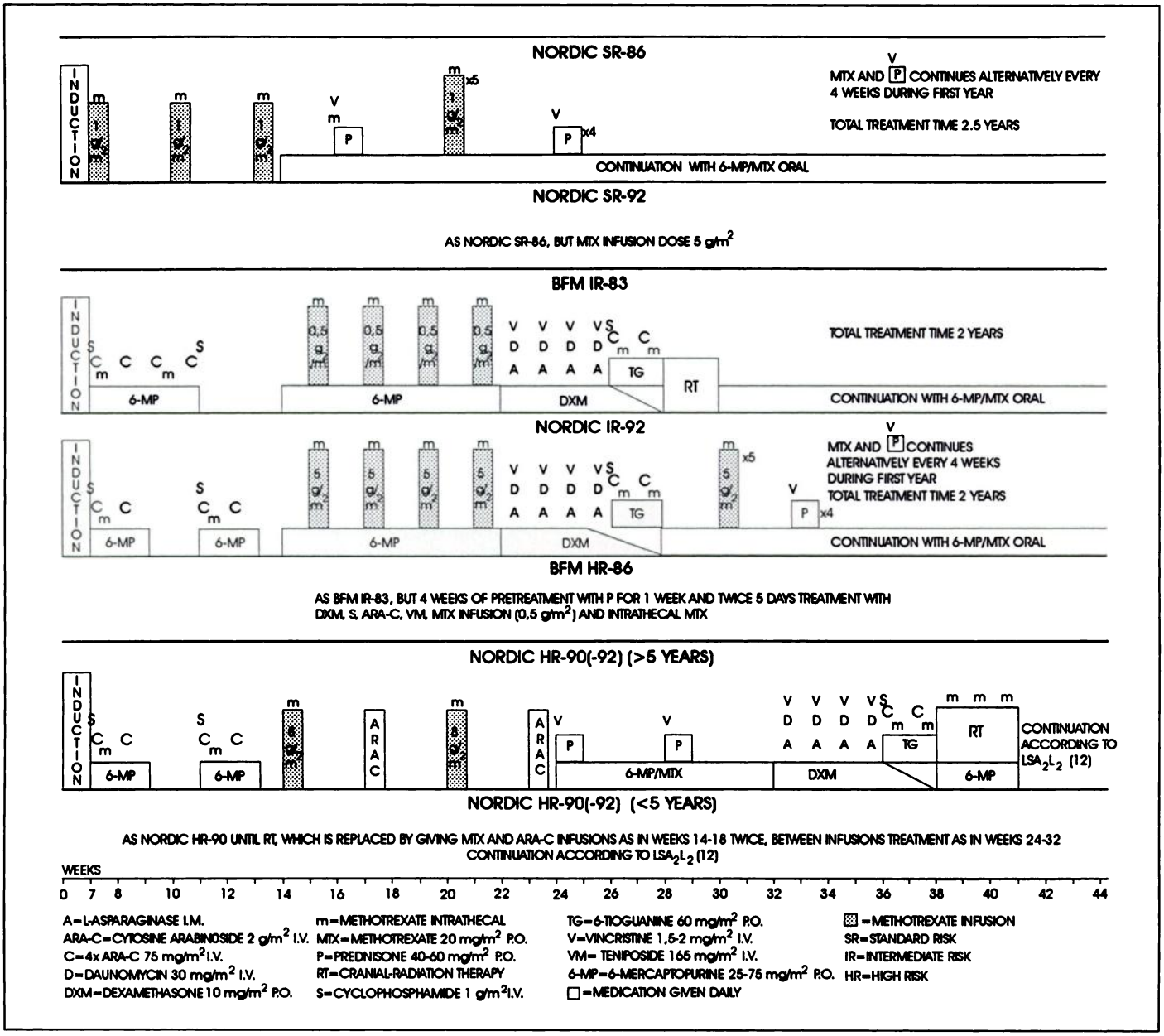

FIGURE 1. Treatment regimens.

the literature (*13*). The images were evaluated knowing that the patient had leukemia but without being aware of the treatment protocol or whether the examination was performed before, during or after treatment.

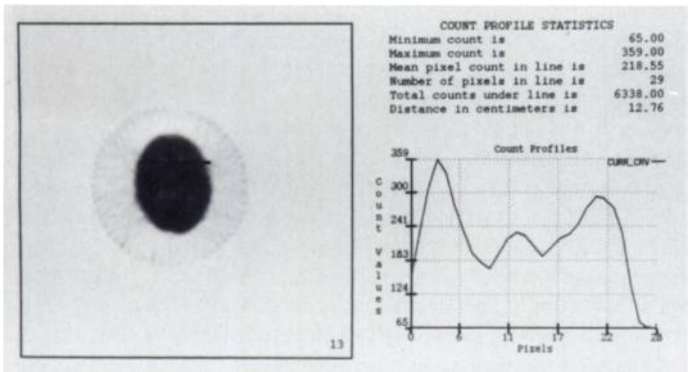

FIGURE 2. An example of a count profile curve. The difference between hemispheres is 19%.

Cranial MRI

Cranial MRI was performed using a 1.0 T superconducting unit. Standard T2-weighted 5-mm axial images, 2300/1590/1 (TR/TE/excitations), were obtained for 11 patients, and T2-weighted, turbo spin-echo images, 3500/1993/1, were obtained for 14 patients. In addition, 3-mm sagittal, T1-weighted (500/15/2) and 5-mm coronal, T1-weighted images (690/15/2) were obtained in all but one patient, who had T2-weighted coronal (2300/1590/1) and T1-weighted (600/15/2) axial scans. Images were analyzed by two radiologists, paying special attention to high intensity white matter changes on the T2-weighted images.

Clinical Examinations

Neuropsychological assessment was performed by the same neuropsychologist during four 45-min sessions according to NEPSY® (*14*). The intelligence quotient was measured with the Wechslers WPPSI (*15*),WISC (*16*) or WAIS (*17*) intelligence test depending on the patient's age. A neurological examination according to Touwen (*18*) was performed on every patient.

TABLE 2
Clinical Data

Patient no.	Age at Dx (yr)	Treatment protocol	CRT (Gy)	MTX i.v. (g/m^2)	MTX i.t. injections	Brain SPECT (tracer, location and percentage of the difference)	MRI brain	Findings	Neuropsychological impairment/hemisphere
1	5.0	Nordic 1986 SR	—	8 × 1	13	HMPAO, left posterioparieto-occipital*	N		Auditive repeating and narration impaired, moderate/left
2	3.5	Nordic 1986 SR	—	8 × 1	13	HMPAO, left temporal 14%	N		Serial functions impaired, VIQ/PIQ 114/127 mild/left
3	3.8	Nordic 1986 SR	—	8 × 1	13	HMPAO, left posterioparietal 17%	N	Motor clumsiness	Verbal functions extensively impaired, VIQ/PIQ 85/106, moderate/left
4	4.1	Nordic 1986 SR	—	8 × 1	13	ECD, left basofrontal and right striatum*	N	Motor clumsiness	Auditive repeating impaired, attention deficit, moderate/frontal
5	2.7	Nordic 1986 SR	—	8 × 1	13	HMPAO, left temporal 15%	N		Mild visuomotoric difficulties, VIQ/PIQ 114/100, mild/right
6	5.5	Nordic 1986 SR	—	8 × 1	13	ECD†, right parieto-occipital 17% and striatum	WMC	Dysdiadochokinesia Balance difficulties	Bilingual, not included
7	5.0	Nordic 1992 SR	—	8 × 5	13	ECD†, left frontal and parietal 17%	N		Not tested
8	10.0	BFM 1986 IR	18	4 × 0,5	9	ECD, right parieto-occipital*	N		Memory impairment, visuospatial difficulties, moderate/right
9	5.5	BFM 1986 IR	18	4 × 0,5	9	ECD, left parietal 12%	N	Motor clumsiness	Impaired memory and verbal functions, VIQ/PIQ 94/110, mild/left
10	3.8	BFM 1986 IR	18	4 × 0.5	9	ECD†, left striatum 25% and left basotemporal 14%	WMC	Dysdiadochokinesia Motor clumsiness	Normal
11	2.9	Nordic 1992 IR	—	9 × 5	13	ECD, left parieto-occipital 8%	N	Motor clumsiness	Normal

*Semiquantification not available because of disk error.
†Examination done with ADAC gamma camera, otherwise with Siemens.
CRT = cranial radiation therapy; MTX = methotrexate; SR = standard risk; IR = intermediate risk; HR = high risk; N = normal; WMC = white matter changes; VIQ/PIQ = verbal/performance intelligence quotient.

Statistical Analysis

The differences between the means for the groups were analyzed using independent samples Student's t-test. A two-tailed p-value below 0.05 was considered significant.

RESULTS

Eleven of the 25 patients had an abnormal SPECT scan (Table 2, Fig. 3), eight of whom had received chemotherapy alone, and three patients presented with cranial irradiation. All of these patients were treated according to the standard or intermediate risk protocol, while all the patients treated according to the high-risk protocol had a normal brain SPECT image. The total amount of intravenous methotrexate received by the patients with abnormal SPECT scans and an average single dose was smaller than that for patients who had normal SPECT scans, but the former had had more frequent methotrexate infusions. The mean time since the last methotrexate infusion did not differ between the groups. The mean ages of the patients with abnormal SPECT scans at the time of diagnosis and evaluation were lower than those of patients with normal SPECT scans (Table 3).

Two patients in the chemotherapy group with abnormal SPECT had small bilateral white matter changes in cerebral MRI, which located separately from the SPECT changes. There were no focal clinical findings in the neurological examination, although motor clumsiness and dysdiadochokinesia were common (Table 2).

Impairment in neuropsychological functioning was found in 19 of 22 patients tested: 10 mild, 8 moderate and 1 serious impairment. The most common findings were impairment of verbal functions (difference between performance and verbal intelligence quotient greater than 10 points in 9 patients and greater than 15 points in 6) and impairment of memory function (eight patients). No significant difference in the results of intelligence testing between the patients with normal and abnormal SPECT scans (Table 4) was found, but the irradiated patients had significantly lower scores for picture completion and block design than the nonirradiated ones. The location of the perfusion defects was associated with the neuropsychological findings in six patients (Patients 1, 2, 3, 4, 8 and 9). There was no association in one patient (Patient 5), two patients with perfusion defects had normal neuropsychological findings and two were not tested (Table 2).

DISCUSSION

SPECT provides a suitable method for investigating brain perfusion in children. It is painless, noninvasive and usually does not require sedation. Almost half of the patients treated for

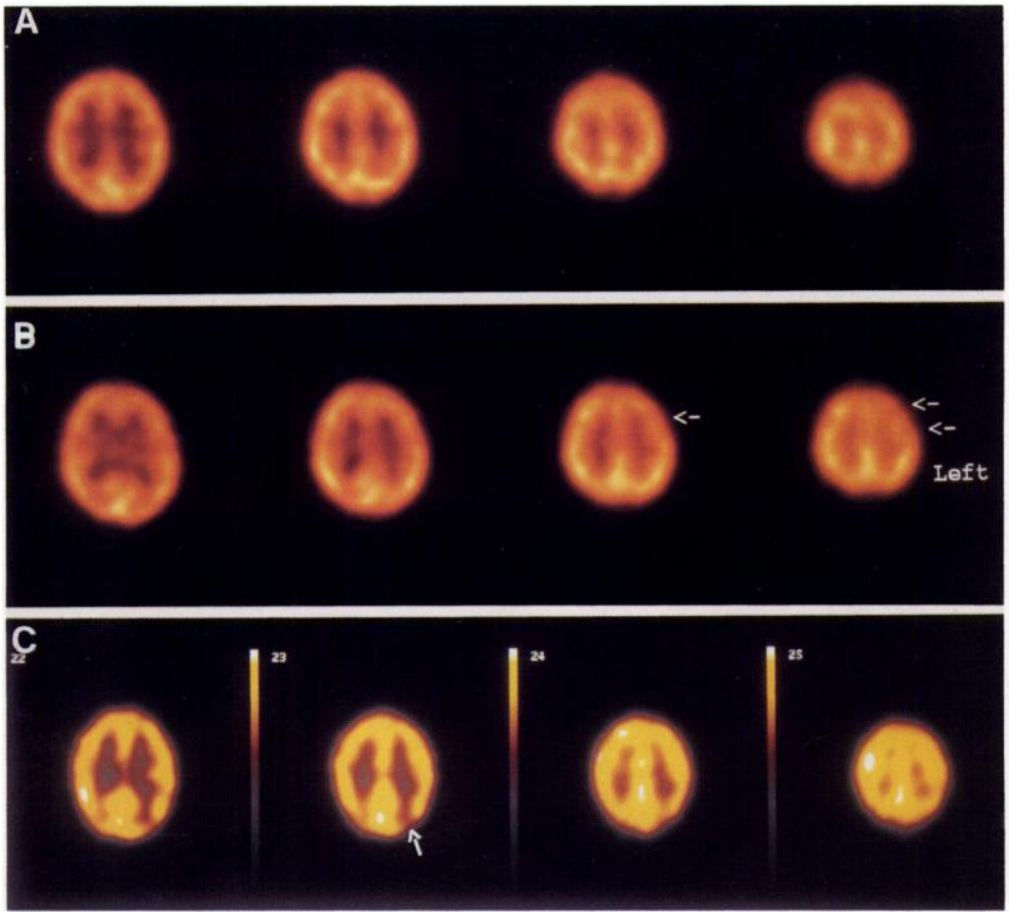

FIGURE 3. Brain perfusion findings in patients with childhood ALL after treatment. (A) Normal ^{99m}Tc-ECD brain SPECT scan. (B) Abnormal ^{99m}Tc-ECD brain SPECT scan with perfusion defects in the frontal and the parietal parts of the left hemisphere (arrows). The difference in the parietal region in semiquantification was 17%. (C) Abnormal finding in a ^{99m}Tc-HMPAO brain SPECT scan with a perfusion defect of 17% in the left posterioparietal region (arrow).

ALL in our series had abnormal SPECT scans, which were indicative of brain perfusion defects. Radiation therapy does not explain these occurences, as only 3 of the 11 patients affected underwent that particular treatment. Most of the drugs used, except for methotrexate, cytosine arabinoside and corticosteroids, do not pass through the blood-brain barrier and are therefore unlikely causative agents for these changes (*19*).

TABLE 3
Characteristics of Patients with Abnormal and Normal SPECT Scans

Variable	SPECT abnormal (n = 11)	SPECT normal (n = 14)	Statistics†
Age at diagnosis (yr)*	4.7 (2.0)	7.2 (4.0)	p = 0.056
Age at evaluation (yr)*	7.7 (2.1)	10.5 (4.0)	p = 0.032
Risk groups (patients):			
Standard risk	7 (63%)	2 (14%)	
Intermediate risk	4 (36%)	1 (7%)	
High risk	0	11 (79%)	
Cranial radiation therapy (patients)	3	10	
Intravenous methotrexate (g/m^2)*	12.6 (15.0)	23.4 (12.4)	p = 0.06
Number of methotrexate infusions*	7.0 (1.9)	3.9 (2.6)	p = 0.03
Number of intrathecal methotrexate injections*	12.2 (1.9)	13.2 (2.2)	p = 0.23
Years since last MTX infusion*	2.1 (0.7)	1.8 (0.8)	p = 0.34
Neuropsychological examination			
Normal	2 (22%)	1 (8%)	
Mild impairment	3 (33%)	7 (53%)	
Moderate impairment	4 (44%)	4 (31%)	
Serious impairment	0	1 (8%)	
Not tested	2	1	

*mean (s.d.)
†Independent samples t-test, two-tailed p-value.

We assume that methotrexate could be responsible for the perfusion defects. It may cause acute transient symptoms of somnolence, confusion and seizures (*20*), and stroke-like episodes have been reported after intravenous methotrexate treatment in patients with osteosarcoma (*7*). Depression of cerebral glucose metabolism has been observed after high-dose methotrexate treatment (*3,4*), as have transient white matter changes in MRI of the brain (*2*). After methotrexate infusion, cerebral blood flow was reduced in an animal experiment (*9*).

The mechanism causing methotrexate neurotoxicity is still not fully understood, but it is thought to be multifactorial. It may disturb at least two important metabolic pathways in the central nervous system. By inhibiting dihydrofolate reductase, methotrexate depletes the cell of its de novo synthesis of purine nucleotides and thymidylate (*21*), and it also appears to inhibit dihydropteridine reductase and thus tetrahydrobiopterin synthesis, which is needed in the initial steps of biogenic amine synthesis (*22*). Many biogenic amines are vasoactive and capable of adjusting the tone of the brain blood vessels and may thereby alter brain perfusion (*23*). It is also possible that methotrexate has a direct toxic effect on the blood vessels by causing damage to the endothelial cells (*8*).

Surprisingly, the occurrence of perfusion defects was not dependent on the intravenous methotrexate dose: A single administered dose was greater in the patients with normal SPECT scans, most of whom received a dose of 8 g/m^2, usually twice, while the patients with abnormal SPECT received a dose of 0.5–5 g/m^2 more frequently, mostly eight times. On the other hand, the total amount of intrathecal methotrexate and the number of intrathecal injections did not differ significantly. The

TABLE 4
Results of the Intelligence Tests: WPPSI, WISC and WAIS Scaled Score Results for Subgroups of Patients*

Variable test points mean (s.d.)	Radiated (n = 12)	Nonradiated (n = 10)	Statistics† Radiated/ Nonradiated	Abnormal SPECT (n = 9)	Normal SPECT (n = 13)	Statistics† Abnormal/ Normal SPECT
Wechsler scales						
Full-scale IQ	109, 2 (8, 4)	113, 7 (9, 3)	ns	110, 6 (9, 1)	111, 7 (9, 1)	ns
Verbal IQ	107, 1 (10, 9)	108, 7 (10, 2)	ns	107, 6 (11, 0)	108, 0 (10, 3)	ns
Performance IQ	109, 8 (11, 1)	116, 4 (11, 3)	ns	111, 9 (9, 6)	113, 5 (12, 9)	ns
Picture						
Completion	10, 2 (2, 1)	12, 7 (1, 9)	p = 0.008	11, 9 (2, 8)	10, 9 (2, 0)	ns
Arrangement	11, 2 (3, 3)	11, 2 (2, 0)	ns	10, 0 (1, 5)	12, 0 (3, 1)	ns
Block design	11, 8 (2, 5)	14, 0 (2, 5)	p = 0.046	13, 4 (2, 5)	12, 3 (2, 8)	ns
Object assembly‡	12, 3 (3, 1)	12, 0 (3, 4)	ns	11, 6 (3, 0)	12, 5 (3, 3)	ns
Coding‡	12, 1 (2, 3)	11, 9 (2, 8)	ns	11, 6 (2, 5)	12, 3 (2, 5)	ns

*Data are mean ± s.d.
†Independent samples t-test, two-tailed p-value.
‡No results for two preschool patients tested with WPPSI.

repeated exposure to intravenous methotrexate, which was always combined with intrathecal methotrexate, may explain the perfusion defects, possibly through the consequences of repeated reductions in local cerebral blood flow, from which the frequent administration of the drug would not have allowed the brain to recover. Our finding is supported by a treatment trial in which frequent administration of intravenous methotrexate was found to carry with it a danger of increased neurotoxicity (*24*).

A high dose of intravenous cytosine arabinoside, which may cause seizures, cerebral dysfunction and acute cerebellar syndrome through an unknown mechanism (*25*), are included only in the high-risk protocol, and, therefore, cannot be responsible for the perfusion defects discussed here.

Corticosteroids reduce vasogenic edema probably through direct vasoconstriction of the cerebral blood vessels and are capable of causing reversible changes resembling atrophy on CT scans (*26*). They reduce blood-brain permeability (*27*), and in animal experiments, dexamethasone can protect neonatal rats from ischemic brain changes (*28*). Dexamethasone, which penetrates into brain tissue more readily than does prednisolone (*29*), is included in the high and intermediate risk protocols, and most of the patients with normal SPECT scans received it. There were four patients with abnormal SPECT scans who had also received dexamethasone, but the other seven patients with abnormal SPECT scans belonged to the standard risk group and received only prednisolone, although for a longer period than high-risk patients. Thus, the protective effect of dexamethasone cannot be excluded.

When the patients are classified according to the international criteria, also used in the Nordic countries, a greater number of younger children are treated according to the standard and intermediate risk protocols, which includes frequent doses of intravenous methotrexate. This could explain the concentration of brain perfusion abnormalities in the younger age group. Children under 5 yr are known to be more sensitive to the effects of cranial radiation therapy (*1*), and the young developing brain with incomplete myelinization may also be more sensitive to the neurotoxicity of chemotherapy.

The fact that brain SPECT exposes the patient to a small dose of radiation makes it difficult to obtain normative data on healthy children, and thus the criteria for abnormality used here are based on adult values and on the literature. Unfortunately, we do not have data from baseline examinations of these children, but in our prospective trial, we examined nine children with ALL before any treatment and found eight SPECT scans to be normal; one patient had small bilateral parietal perfusion defects (unpublished data). Brain SPECT gives information only on actual blood-brain perfusion, and the stability of cerebral perfusion abnormalities remains to be ascertained. Unfortunately, it is not possible to evaluate overall brain perfusion levels quantitatively with SPECT without arterial blood samples. However, PET studies have shown the overall glucose metabolism to be reduced after leukemia treatment (*3*), and perfusion was reduced in all brain regions in an experiment with rats (*9*). Many of the brain perfusion defects were located in the watershed region between the great arteries, areas that are most vulnerable to diminished perfusion. This further supports the idea that the overall perfusion level may also be diminished in these patients.

The perfusion defects observed in SPECT were not associated with the appearance of more severe impairment in the neuropsychological examination, but some conformity of location and hemisphere was found between the SPECT abnormalities and neuropsychological findings in most of the patients. The verbal functions in the left hemisphere of the brain are developing quickly during the first years of life, when most of the patients with abnormalities were exposed to the neurotoxic drugs. It is believed that the actively developing brain region of the child is more vulnerable to injury. This could give an explanation to our more frequent findings in the left hemisphere. The plasticity of the young developing brain and the capacity for shifting functions to other brain regions (*30*) may partially explain the instances of differences between the perfusion and neuropsychological findings. It is also known that the long-term neurotoxic effects of the central nervous system treatment may be delayed and progressive (*6*).

No focal neurological signs were observed in the clinical neurological examination. Motor clumsiness and dysdiadochokinesia may be signs of impaired central nervous system function, or of peripheral neuropathy, which is a well-known sequela of leukemia treatment, especially when vincristine is used (*31*).

Brain SPECT was more sensitive than MRI for detecting treatment-related neurotoxicity. Perfusion MRI, which is possible with new high-performance magnets, can detect brain

ischemia in cases of cerebrovascular disease and could probably be used to detect treatment-induced perfusion defects (*32*).

CONCLUSION

This preliminary finding of brain perfusion impairment in patients with ALL needs confirmation in a prospective follow-up investigation in combination with perfusion MRI and/or PET perfusion or glucose studies. Methotrexate chemotherapy may be preferable as a central nervous system treatment for ALL, but its extensive use may have unexpected neurotoxic complications. Central nervous system treatment is essential, but it is important to know the long-term neurological sequelae when trying to develop the best treatment available at the least cost.

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