Computed tomography of the brain following prophylactic treatment with irradiation therapy and intraspinal methotrexate in children with acute lymphoblastic leukemia

Elisabeth Lund¹ and Bente Hamborg-Pedersen²
Departments of ¹Neuroradiology and ²Pediatrics, Aarhus Municipal Hospital, Aarhus, Denmark

Summary. In 28 children with acute lymphoblastic leukemia (ALL) computed tomography (CT) was performed in order to demonstrate possible cerebral changes following treatment with prophylactic irradiation and intraspinal methotrexate (MTX). The time of CT-scan examination varied from 1 year and 1 month to 10 years and 1 month after diagnosis of ALL. The age of the children ranged from 3 years and 11 months to 14 years and 5 months. Six children had normal CT scans, 12 children had slight atrophy-like changes, and nine had severe cerebral atrophy. Two patients in the latter group presented an enlarged ventricular system as well. In one patient intracerebral calcification was the only pathologic finding. The severe changes were seen in children of all age groups, but predominantly in children with a short duration of their disease, severe symptoms, and frequent marrow relapse. Changes induced by steroid therapy may be reversible. No satisfactory explanation of the demonstrated cerebral pathologic findings can be given, except that they are the consequences of the combination of total therapy and severity of disease in the individual patient. Measurement of attenuation coefficients in grey and white matter shows increasing values with age during childhood. A combination of decreasing attenuation coefficients, especially in the white matter, and the finding of severe atrophy seems to be a bad prognostic sign.

Key words: Leukemia – CNS prophylaxis – atrophy – intracerebral calcifications – attenuation coefficients – cerebral irradiation

In the late sixties after progress in cytostatic treatment, the prognosis in children with acute lymphoblastic leukemia (ALL) was improved. However, at the same time an increasing number of children developed signs of leukemic disease in the central nervous system [21]. This complication causing death in about 50% of the children is due to restraint by the blood-brain barrier of the transfer of cytostatic drugs into the brain tissue. Accordingly for several years a combination of prophylactic irradiation therapy of the central nervous system (CNS) and intraspinal methotrexate (MTX) has been part of the treatment schedule in ALL. However, as demonstrated in several reports [1-17] CNS prophylaxis may involve a considerable risk of secondary brain damage. Cerebral atrophy, demyelinization, leucoencephalopathy and intracerebral calcifications have been demonstrated by computed tomography (CT) and also confirmed by autopsy in several cases.

It has not been established how these pathologic anatomic changes in the brain develop. They may be caused by MTX, irradiation therapy, a combination of both, or other factors, as perhaps the general condition of the patient: the nature of his disease and his nutritional state may be influential. Being an antagonist to folinic acid MTX interferes with the formation of myelin and DNA synthesis [7-9]. This is enhanced by irradiation, which brings about a more or less severe destruction of the blood-brain barrier protection. As a result changes in the concentrations of protein, glucose and enzymes in the spinal fluid may be seen during this treatment [6].

The purpose of the present investigation is to demonstrate possible cerebral pathologic findings in a number of children with ALL, subjected to prophylactic irradiation therapy and intraspinal MTX.
Material and methods

The diagnosis of ALL was made between 1971 and 1981 and the patients comprise only children without verified CNS leukemia at the time, when CT scan was first performed.

The material comprises 28 children (11 girls and 17 boys), whose age ranged from 3 years and 11 months to 14 years and 5 months at the time of CT scan.

With few exceptions the patients received therapy according to the following schedule after the diagnosis of ALL was made.

**Induction treatment:** Prednisone 180 mg perorally/1 m² body surface area/24 h for 6 weeks. Vincristine 1.5 mg intravenously/1 m² body surface area/1 week for 6 weeks (maximum). Adriablastine 30 mg intravenously/1 m² body surface area/1 week for 3 weeks (maximum).

**CNS prophylaxis** (combined with induction treatment): MTX 12 mg by lumbar puncture/1 m² body surface area/1 week for 6 weeks. Irradiation therapy at a total of 2.400 R for the last 3 weeks of prophylaxis.

**Maintenance treatment** (given for 3 years): Mercaptopurine perorally 75 mg/1 m² body surface area/24 h. MTX perorally 20 mg/1 m² body surface area/1 week.

Induction treatment was repeated in case of bone marrow relapse, supplemented by MTX intraspinally if necessary.

All CT scans have been performed within 1 year from 1981 to 1982 in children who were in clinical remission. The time interval between diagnosis of ALL and CT scan examination ranges from 1 year and 1 month to 11 years and 2 months. At the time of examination the patients were all in a good general condition and nutritional state and they were not anemic.

The CT scans were performed using a DELTA-OHIO 25 scanner with 8 mm slices and a Gantry-angulation of -10° in relation to the meatoorbital line when possible. In addition most of the patients were scanned after contrast (Conray 400, 1 ml/kg body weight intravenously) as well.

The scannograms have been evaluated as regards presence of cerebral calcification and leukemic infiltrations in meninges and brain tissue. The widths of visible cortical sulci and size of the ventricular system have been estimated according to the criteria given by Enzman and Lane [27], Takao et al. [25], and Petersen et al. [26]. There seems to be some disagreement on the scannographic presentation of cortical sulci before the age of 15 years. In consequence the average width of the three widest sulci has been registered in the following way: Nonvisible cortical sulci = normal, sulci < 3 mm = slight "atrophy", sulci > 3 mm = severe "atrophy". The Sylvian sulcus has been regarded as normal, if it is < 4 mm and the frontal interhemispheric distance as normal if < 2 mm. Ventricular size using Evans ratio is normally < 0.31 in children aged 3 years or more. The width of the third ventricle is normally < 6 mm.

In all patients supplementary high window-level exposures were made in order to discover leukemic foci in the skull.

The attenuation values before injection of contrast have been measured bilaterally in the following regions (Region of Interest corresponding to 20 pixels): The white matter anterior to the frontal ventricular horn, in centrum semiovale and at the genu of the internal capsule. Attenuation values in the grey matter have been measured interhemispherically in the frontal and parietal regions and also in the lentiform nucleus and at the head of the caudate nucleus.

Results

Clinical and therapeutic data are given in Table 1. Age at the time of diagnosis of ALL ranges from 1 year and 4 months to 11 years and 2 months. At the time of their CT scan 13 patients still received maintenance therapy. Five patients had steroids within 3 months before scanning. One of these children was still receiving steroids at the time of the examination (patient 28 (JS)). In the three patients who have the longest survival time (patients 5 (HEH), 13 (HJ) and 17 (BH)) almost 3 years elapsed before irradiation therapy was given. They also received a high total dose of MTX intraspinally. This was due to a change in treatment schedule after the introduction of prophylactic CNS irradiation. Six patients developed a marrow relapse, four of these before CT examination, two children patients 20 (BHJ) and 27 (SAH) 1 and 6 months after the scan, respectively. Two patients with relapse patients 27 (SAH) and 28 (JS) had repeated CT scans, one of them (SAH) developed CNS leukemia.

The results of the CT scan are also shown in Table 1. Six patients were normal (Fig.1), 12 patients had slight cortical "atrophy" (+), and 9 patients exhibited severe cortical "atrophy" (++). In 2 patients and enlarged ventricular system was seen as well (patients 27 (SÅH) and 28 (JS)). Apart from one patient (patient 26 (ABH)) with a very long survival, the most severe atrophy was seen in children with a short duration of their disease, but irrespective of their age. This appears from Figure 2 which shows the rela-