Studies of cerebral blood flow and cerebrospinal fluid in childhood acute lymphoblastic leukemia

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I. Österlundh G, Bjure J, Lannering B, Kjellmer I, Uvebrant P, Márky I. Studies of cerebral blood flow in children with acute lymphoblastic leukemia: Case reports of six children treated with methotrexate examined by single photon emission computed tomography. *J Pediatr Hematol Oncol* 1997;19:28-34.

II. Österlundh G, Bjure J, Lannering B, Kjellmer I, Uvebrant P, Márky I. Regional cerebral blood flow and neuron-specific enolase in cerebrospinal fluid in children with acute lymphoblastic leukemia during induction treatment. *J Pediatr Hematol Oncol* 1999;21:378-383.

III. Österlundh G, Kjellmer I, Lannering B, Rosengren L, Nilsson UA, Márky I. Neurochemical markers of brain damage in cerebrospinal fluid during induction treatment of acute lymphoblastic leukemia in children. *Pediatr Blood Cancer* 2008;50:793-798.

IV. Österlundh G, Sixt R, Uvebrant P, Márky I. Regional cerebral blood flow in children examined by SPECT five years after treatment of acute lymphoblastic leukemia. *(submitted).*

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and more than 80% of the patients are cured today. Treatment might cause side effects and central nervous system (CNS) irradiation has been replaced by systemic high-dose methotrexate (MTX) and intrathecal (IT) MTX due to the risk of late effects. However, treatment without CNS irradiation is also neurotoxic and might cause brain damage.

Three patients developed subacute neurotoxicity, one after IT MTX and two after HDMTX including IT MTX. All showed impaired regional cerebral blood flow (rCBF) when examined by single photon emission computed tomography (SPECT). The patients improved within a few days during treatment with the Ca^{2+}-channel blocker nimodipine and all recovered completely. Another three patients, without neurological symptoms, were examined at different phases of ALL treatment and all had disturbances in rCBF. The heterogeneous cerebral hypoperfusion was however less pronounced than in the patients with symptoms.

Twenty-five patients were examined during remission induction with prednisolone, doxorubicin, vincristine and IT MTX. Sixteen of these patients were first examined before start of treatment and nine during the first week. None had any neurologic symptoms but rCBF had deteriorated in all patients when re-examined after four weeks. The nine patients examined during the first week had heterogeneous cerebral hypoperfusion already at the first examination but to a lesser degree than at four weeks when the two groups showed similar results. Fourteen of the twenty-five patients were re-examined seven years later, i.e. five years after cessation of treatment. Eleven had normalized rCBF, one had improved, one was unchanged and the last one had sequelae after a stroke.

Impact on CNS can also be studied by analyzing neurochemical markers of brain damage in cerebrospinal fluid (CSF). Samples were collected before start of treatment, at day 8, at day 15 and at day 29. The levels of three brain specific proteins increased during remission induction indicating damage to neurons and glia cells. Neuron-specific enolase (NSE), a marker of neurons, reached the highest level at day 8. Glia fibrillary acidic protein (GFAp), a marker of astrocytes, and the light subunit of neurofilament protein (NFp), a marker of axons, reached the highest level at day 29. Analyses of ascorbyl radical (AsR) as a marker of oxidative stress were not conclusive.

Key words: Childhood acute lymphoblastic leukemia, methotrexate, neurotoxicity, cerebral blood flow, single photon emission computed tomography, cerebrospinal fluid, neuron-specific enolase, glia fibrillary acidic protein, neurofilament, ascorbyl radical

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