Leukoencephalopathy Following High-Dose Intravenous Methotrexate Chemotherapy: Quantitative Assessment of White Matter Attenuation Using Computed Tomography

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Summary. A clinical or subclinical leukoencephalopathy occurs in some children after treatment of acute lymphatic leukemia with prophylactic cranial radiation therapy and parenteral or intrathecal methotrexate. We have observed a similar clinical leukoencephalopathy in patients with bone tumors treated with intravenous high-dose methotrexate and citrovorum factor without cranial irradiation. CT scans of such patients may indicate decreased white matter attenuation, but visual appraisal of this phenomenon is occasionally misleading. A computerized method for analyzing white matter hypodensity by determining the mean attenuation coefficient for one or several contiguous CT slices has therefore been developed. Serial comparisons of this mean attenuation coefficient appear to be more reliable than simple visual appraisal.

A chronic, progressive leukoencephalopathy may affect some children with acute lymphatic leukemia (ALL) treated with parenteral and intrathecal methotrexate (MTX-IT) as well as prophylactic whole-brain radiation [5]. The disorder usually begins with subtle personality or behavioral changes followed by seizures, ataxia, dysarthria, spastic quadraparesis, and dementia. We have observed a similar leukoencephalopathy in osteosarcoma patients receiving high-dose intravenous methotrexate (MTX-HD) and citrovorum rescue without cranial radiation therapy, indicating that cranial irradiation is not always necessary for the development of this neurologic disorder. Decreased white matter attenuation observed on CT scans is commonly regarded as a diagnostic sign of leukoencephalopathy. However, in our experience visual assessments of white matter hypodensity have been unreliable.

This report describes a new computerized method for quantifying the extent of white matter alteration. Preliminary data suggests that this method may be more reliable than visual inspection.

Materials and Methods

Case Report: A. W.

This 14-year-old white male was referred to Memorial Sloan-Kettering Cancer Center with progressive pain and swelling of the right ankle and multiple pulmonary metastases related to a malignant bone sarcoma. Chemotherapy was instituted with bleomycin, cyclophosphamide, and actinomycin D, followed by escalating doses of MTX-HD (up to 20 g/m²) and citrovorum rescue; vincristine (2 mg/m²) was administered simultaneously. The MTX-HD regimen was repeated approximately every 10 days.

After 3 months the child became lethargic, disinterested, and confused. He complained of recurrent episodes of left-sided sensory phenomena consisting primarily of acral paresthesiae. On one occasion these paresthesiae were accompanied by a brief loss of consciousness, followed by a transient dysarthria and left hemiparesis. Subsequently he was treated with Dilantin for a presumed seizure disorder. An EEG scan performed 16 weeks after the initiation of MTX-HD chemotherapy revealed mild decreased attenuation of the centrum semiovale (Fig. 1).

MTX-HD therapy was continued and during the ensuing 4 weeks the patient became more encephalopathic, incontinent, and quadraparetic. He began to experience intermittent right-sided paresthesiae, developed a profound dementia and ultimately lapsed into stupor.

After each course of MTX-HD, 24-, 48-, and 72-h serum MTX levels were in the 'nontoxic' range, and there was no evidence of systemic MTX toxicity. However, a CSF MTX level obtained 8 days after the 10th course of MTX-HD therapy at a time when the patient was clinically encephalopathic was 0.51 x 10⁻⁸ M.¹

The EEG was diffusely slow and a CT scan at 20 weeks (Fig. 1) revealed a further decrease in white matter attenuation.

Consequently large doses of intravenous citrovorum were administered and methotrexate therapy withheld. The patient gradually improved over the next 12 months and remains moderately demented, grossly dysarthric, and mildly quadraparetic. Psychometric testing (WISC) performed 12 months after the initiation of MTX-HD therapy indicated an IQ of 75, and a contemporaneous CT scan revealed marked hydrocephalus (Fig. 2).

¹ Following a single course of MTX-HD, MTX is normally undetectable in the CSF by the 4th day post treatment (Mehta and Rosen, personal communication)
Quantitative CT Analysis

CT scans were performed on a DeltaScan-50 body scanner or a DeltaScan-25 dedicated head scanner and image data stored on magnetic tape. In order to quantitate changes in white matter attenuation, we determined the mean attenuation coefficient (MAC) for single CT brain slices, utilizing the DeltaPlan RT System diagnostic software package. Regions of interest were selected to include all of the brain parenchyma lying within the confines of the skull, and the attenuation coefficients of individual volume elements (voxels) were computer binned according to Delta number (Fig. 3). MACs for specified data ranges (chosen so as to include all CSF and white matter voxels) were then calculated, taking into account the appropriate drift corrections.

When comparing the frequency histograms of different CT brain slices (Fig. 3), one must take into account small day-to-day variations in the measured X-ray attenuation coefficient for water. Since, in our experience, the MACs for water obtained by scanning water phantoms are unreliable (i.e., they do not accurately reflect the X-ray absorption density of water within the brain as measured on patient CT scans), we devised a water correction based upon the assumption that the magnitude of the observed scan-to-scan drift may be inferred from the translation of computer-generated histograms relative to one another along the \( \Delta \)-axis of an \( n \) versus \( \Delta \) plot (Figs. 3 and 4). This correction was determined by comparing the bin numbers of different histograms corresponding to the same cumulative percentage of voxels (Fig. 4). For example, if (i) histograms A and B each contain 1000 voxels, (ii) in histogram A the voxel with the 25th smallest Delta number falls into bin No. 500, whereas the corresponding voxel in histogram B falls into bin No. 503, and (iii) this relationship is maintained when A and B voxels with the 50th, 100th, etc., smallest Delta numbers are compared, then one can conclude that histogram is translated three bins to the right along the \( \Delta \)-axis relative to histogram A.

Our drift correction must be applied to the data range of one of the two histograms being compared as well as to the MAC calculated for that data range. In general, we compared the corrected MACs of corresponding pairs of slices from different CT scans (Table 1). However, on one occasion, the histograms from seven contiguous slices from each of two CT scans performed on the same patient were computer summed, bin by bin, and the