Elevation of Homocysteine and Excitatory Amino Acid Neurotransmitters in the CSF of Children Who Receive Methotrexate for the Treatment of Cancer

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Purpose: **Folate deficiency, either by diet or drug, increases plasma homocysteine (Hcy). Hcy damages cerebrovascular endothelium, and hyperhomocysteinemia is a risk factor for stroke. Hcy is metabolized to excitatory amino acid (EAA) neurotransmitters, such as homocysteic acid (HCA) and cysteine sulfinic acid (CSA), which may cause seizures and excitotoxic neuronal death. We postulated that excess Hcy and EAA neurotransmitters may partly mediate methotrexate (MTX)-associated neurotoxicity.**

Patients and Methods: **In this retrospective analysis, we used high-performance liquid chromatography (HPLC) to measure Hcy, HCA, and CSA in CSF from two groups of children: (1) a control group of patients with no MTX exposure, and (2) a treatment group of patients who had received MTX no more than 7 days before a scheduled lumbar puncture.**

Results: **The treatment group had a significantly (P = .0255) greater concentration of Hcy in CSF (0.814 μmol/L ± 0.215 [mean ± SEM], n = 23) than the control group (0.210 μmol/L ± 0.028, n = 34). HCA and CSA were not detected in CSF from control patients (n = 29); however, MTX caused marked accumulation of CSF HCA (119.1 μmol/L ± 32.0, n = 16) and CSA (28.4 μmol/L ± 7.7, n = 16) in the treatment group. Patients with neurologic toxicity at the time of lumbar puncture had many of the highest concentrations of Hcy, HCA, and CSA.**

Conclusion: **These data support our hypothesis that MTX-associated neurotoxicity may be mediated by Hcy and excitotoxic neurotransmitters.**

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METHOTREXATE (MTX) IS A MAINSTAY of therapy for children with acute lymphoblastic leukemia (ALL)[1] and is also used widely in other neoplastic and nonneoplastic disorders. Clinical success notwithstanding, MTX therapy may be associated with significant neurotoxicity of uncertain etiology.[2-5] MTX-associated neurotoxicity is classified in three characteristic forms: acute, subacute, and late. Acute neurotoxicity occurs within 1 day of administration and may be characterized by nausea, emesis, headaches, somnolence, confusion, and seizures. Subacute neurotoxicity typically occurs 7 to 9 days following MTX exposure and manifests variably as seizures, affective disturbances, and focal neurologic deficits, usually transient, including paresis, anesthesia, pseudobulbar palsy, and visual disturbances. Late or chronic MTX-associated neurotoxicity occurs weeks to months following therapy and involves impairment of higher cognitive functions.

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Although MTX has been used for nearly 50 years, the pathogenesis of MTX-associated neurotoxicity remains unclear, although it is likely multifactorial.[6] It has been proposed that this neurotoxicity may be in part mediated by the interference of MTX with the recycling of biopterin species, which thereby impairs synthesis of the neurotransmitters dopamine and serotonin.[7] Studies have demonstrated perturbations in biopterin and neurotransmitter chemistry consequent to MTX exposure temporally correlated with neurologic symptoms[8]; however, these interesting associations require further investigation to establish causality. MTX is also known to promote adenosine elaboration and accumulation.[9] Adenosine has neuromodulatory properties and its accumulation in the CNS is associated with headache, nausea, emesis, and somnolence.[10] We have recently shown that children who receive MTX for leukemia have significant elevations of adenosine in CSF and, when symptomatic, that methylxanthines, which are adenosine receptor antagonists, ameliorate acute toxicity.[11] These models conceivably explain some features of MTX-associated neurotoxicity, but do not adequately account for the occurrence of others, including seizures, focal neurologic deficits, and chronic toxicity.

MTX readily increases plasma homocysteine (Hcy)[12-15] and this increase may be a sensitive and responsive indicator of antifolate therapy. This observation is important, because Hcy is injurious to vascular endothelium[16,17] and hyperhomocysteinemia is a strong, independent risk factor for vascular disease,[18] including stroke and carotid artery stenosis. Since reported consequences of MTX therapy include focal neurologic deficits,[2-5] mineralizing microangiopathy,[19] and radiographic ischemic white mat-

ter changes,[20] ischemic vascular disease may be implicated in the pathogenesis of MTX-associated neurotoxicity. We propose that excess Hcy, in light of its role in vascular injury, may be in part the mediator of this toxicity. Moreover, excess Hcy can be metabolized to sulfur-containing excitatory amino acid (EAA) neurotransmitters, including homocysteic acid (HCA) and cysteine sulfinic acid (CSA), as well as the related compounds homocysteine sulfonic acid (HCSA) and cysteic acid (CA).[21,22] These endogenous agonists of *N*-methyl-D-aspartate (NMDA) receptors are likely important in the genesis of seizures[23] and, further, they may cause neuronal death and late MTX-associated sequelae via their excitotoxic properties.[24,25]

Determination of the CSF concentrations of Hcy and sulfur-containing EAAs in patients who receive MTX would be important to investigate further their roles as mediators of MTX-associated neurotoxicity. There are minimal published data on normal values for CSF Hcy, especially in the pediatric population. Normal ranges for CSF HCA, CSA, HCSA, and CA are not known. We therefore measured the Hcy and sulfur-containing EAA content of CSF from children who received MTX for cancer and from children not previously exposed to MTX. We hypothesized that the concentrations of Hcy and EAA neurotransmitters in the CSF of children who received MTX would be higher than in the control group.

PATIENTS AND METHODS

We conducted a retrospective analysis of stored CSF specimens from patients who had received lumbar punctures at the time of diagnosis of cancer or during the course of its treatment. Also analyzed were stored CSF samples from patients with neurologic disease obtained for diagnostic purposes. For analysis of the data we defined two groups of patients: (1) a control population that included patients without any MTX exposure, and (2) a treatment group that included individuals who had received MTX within the 7 days preceding a lumbar puncture. A cut-off period of 7 days was chosen because many of the patients in this study received MTX according to weekly cycles; moreover, much of the acute and subacute neurologic toxicity associated with MTX occurs within 1 week of exposure.

Informed consent was obtained from all patients (or parents), and MTX was administered according to several disease-specific, institutional review board–approved protocols. All lumbar punctures were obtained under the direction of these protocols; no extra lumbar punctures were obtained for the purposes of this study. Moreover, our frontline institutional protocol for acute lymphoblastic leukemia (since 1986) specifies that the scheduled lumbar puncture is performed at the end of a course of oral divided-dose MTX and before delayed leucovorin is given.[26]

Not all patients had adequate CSF collection for all measurements and matched plasma samples were not available for the majority of the subjects. For patients from whom two separate CSF specimens were obtained, collections were separated by many weeks or months, and no patient had more than two samples of CSF assayed. None of the patients had leukemic CNS disease or exposure to cranial irradiation at the time the samples were obtained.

Following collection, CSF samples were placed on ice at the bedside for transport and then stored at −20°C until they were analyzed. Grossly bloody specimens were excluded from analysis due to the confounding presence of exogenous Hcy.

The control group for Hcy determinations included samples of CSF from 34 children. Of these, 17 had lumbar punctures at the time of diagnosis of leukemia and the remaining 17 had lumbar punctures for the diagnosis of neurologic disease. The corresponding treatment group included 23 samples of CSF from 16 children. Of these 16 children, 15 had received MTX for the treatment of leukemia and one for the treatment of neuroblastoma.

The control group for HCA, CSA, HCSA, and CA measurements included samples of CSF from 29 children; 12 had lumbar punctures at the time of diagnosis of leukemia and the remaining 17 had lumbar punctures for the diagnosis of neurologic disease. The corresponding treatment group included 16 samples of CSF from 12 patients. Of these 12 patients, 11 had received MTX for the treatment of ALL and one for the treatment of neuroblastoma.

CSF Hcy was assayed by high-performance liquid chromatography (HPLC). The tributylphosphine/ammonium 7-fluorobenzo-2-oxa-1,3-diazide-4-sulfonate (TBP/SBD-F) method applied TBP for reduction and SBD-F as derivatization agent according to Araki et al,[27] with the modifications reported by Ling et al[28] for the microbore application, Hyland et al[29] for CSF Hcy signal optimization scheme, and the internal standard quantitation according to Vestor et al.[30] The SBD-F derivatives were eluted isocratically from a Prodigy octadecylsilane (ODS)-3 100A 150- × 1.0-mm 5-μm microbore column (Phenomenex, Torrance, CA). Standards ranged from 5 nmol/L to 2,000 nmol/L. Variance-stabilized regression analysis of calibration standards was used for statistical analysis of data.[31] The standard curve was linear over the range tested (R^2 =.992) with a mean residual of 8%. The within-day and between-day coefficients of variation were determined using a single pooled CSF sample aliquotted into 250-mL portions and left frozen at −20°C.

CSF HCA, HCSA, CSA, CA, and other amino acids were determined by reverse-phase HPLC coupled to electrochemical detection after precolumn derivatization with *o*-phthaldialdehyde (OPA).[32] Modifications to the method were made for the separation and detection of the excitotoxic sulfur amino acids from other amino acids present in CSF samples. Activated OPA reagent was prepared by the addition of 1 μL of 3-mercaptopropionic acid to 200 μL of OPA incomplete reagent solution (Sigma, St Louis, MO). CSF (4 μL) was then reacted with activated OPA reagent, and after exactly 2 minutes, the entire mixture was injected into a Hewlett Packard 1090 gradient liquid chromatograph. The OPA-derivatized amino acids were separated on a reverse-phase C18 Hypersil column (250 mm × 4 mm, 5-μm particle size; Hewlett Packard, Wilmington, DE) and detected by a Coulochem II electrochemical detector equipped with a dual electrode analytical cell, model 5011 with E1 set at +250 mV and E2 set at +700 mV (ESA Inc, Chelmsford, MA). The mobile phase consisted of two eluents: 0.15 mol/L sodium acetate adjusted to pH 5.3 with concentrated acetic acid, finally containing 6% methanol (solvent A), and 0.15 mol/L sodium acetate adjusted to pH 5.7 with concentrated acetic acid, finally containing 70% methanol (solvent B). The flow rate was at 1.3 mL/min and separations were performed at 40°C. Isocratic conditions with 100% solvent A were held at 15 minutes, then solvent B was increased to 100% in 35 minutes. Reequilibration to 100% solvent A lasted 10 minutes before the next sample was injected. Peak identity was confirmed

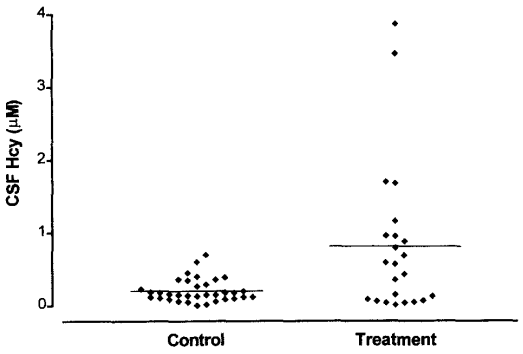

Fig 1. Effect of MTX on CSF Hcy. The treatment group had a significantly ($P = .0255$) greater concentration of Hcy in CSF (0.814 μmol/L ± 0.215 [mean ± SEM], n = 23) than the control group (0.210 μmol/L ± 0.028, n = 34). Horizontal bars represent mean concentrations.

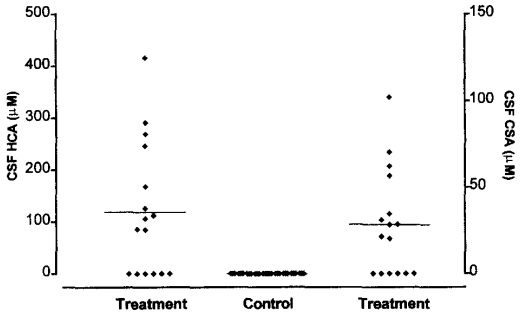

Fig 2. Effect of MTX on CSF HCA and CSA. HCA and CSA were not detected in CSF from controls (n = 29); however, MTX caused marked accumulation CSF HCA (119.1 μmol/L ± 32.0, n = 16) and CSA (28.4 μmol/L ± 7.7, n = 16) in the treatment group. Horizontal bars represent mean concentrations.

by matching retention times based on the retention time of external standards, as well as by coelution after spiking human CSF with authentic standards. The lowest limit of detection for the various OPA-derivatized amino acids varied between 10 and 50 nmol/L using a signal-to-noise ratio of 3.

CSF 5-methyltetrahydrofolate was determined by reverse-phase HPLC coupled to electrochemical detection as previously described.[33]

One- and two-tailed Mann-Whitney tests and linear regression analysis were used for statistical analysis where appropriate.

RESULTS

Hcy is increased in the CSF of patients recently treated with MTX. The concentration of Hcy in CSF from the treatment and control groups is depicted in Fig 1. The control group (n = 34) had a mean Hcy concentration of 0.210 μmol/L ± 0.028 (SEM), a median of 0.155 μmol/L, and a range of 0.003 to 0.700 μmol/L. The treatment group (n = 23) had a mean Hcy concentration of 0.814 μmol/L ± 0.215, a median of 0.567 μmol/L, and a range of 0.008 to 3.862 μmol/L. A one-tailed Mann-Whitney test detected a significant difference between the groups ($P = .0255$).

Sulfur-containing EAA neurotransmitters are increased in the CSF of patients recently treated with MTX. The concentrations of HCA and CSA in CSF from the treatment and control groups are depicted in Fig 2. HCA and CSA were not detected in CSF from the control population (n = 29). The treatment group (n = 16) had a mean HCA concentration of 119.1 μmol/L ± 32.0, a median of 96 μmol/L, and a range of 0 to 416 μmol/L. The treatment group (n = 16) also had a mean CSA concentration of 28.4 μmol/L ± 7.7, a median of 24.9 μmol/L, and a range of 0 to 102 μmol/L. A highly significant correlation between HCA and CSA was detected by linear regression analysis ($R^2 = .99$, $P < .0001$). Also measured were the CSF concentrations of the related compounds HCSA and CA. HCSA (1.31 μmol/L ± 0.38) and CA (0.18 μmol/L ± 0.06) were found in the treatment group (n = 16), but none was detected in controls (n = 29).

Sulfur-containing EAA neurotransmitters are increased in the CSF when CSF Hcy is high. Figure 3 depicts the relationship between CSF Hcy and CSF HCA for all patients who had both compounds measured. No patient whose CSF Hcy was less than 0.355 μmol/L had detectable quantities of HCA. Most patients whose CSF Hcy was ≥ 0.355 μmol/L, and all patients with CSF Hcy

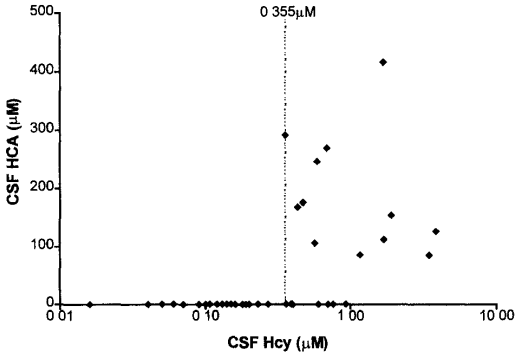

Fig 3. Relationship between CSF Hcy and HCA. No patient whose CSF Hcy was < 0.355 μmol/L (----) had detectable CSF HCA. Most patients whose CSF Hcy was ≥ 0.355 μmol/L, and all patients whose CSF Hcy was > 0.930 μmol/L, had elevated CSF HCA.

Table 1. Effect of MTX on the Concentration of Other Amino Acids in the CSF

Group	Mean ± SEM Value (μmol/L)							
	Asp	Ser	Glu	Gln	Gly	Thr	Arg	Tau
Control (n = 28)	1.6 ± 0.2	14.3 ± 0.8	1.1 ± 0.1	944 ± 27	4.0 ± 0.4	12.2 ± 0.8	10.9 ± 0.7	4.5 ± 0.4
Treatment (n = 16)	1.3 ± 0.2	11.3 ± 1.2	0.6 ± 0.1*	836 ± 121	8.0 ± 0.6†	20.9 ± 2 6*	10.1 ± 1.2	4.0 ± 0.5

Abbreviations: Asp, aspartate; Ser, serine; Glu, glutamate; Gln, glutamine; Gly, glycine; Thr, threonine; Arg, arginine; Tau, taurine.
*$P < .01$.
†$P < .0001$.

levels greater than 0.930 μmol/L, had detectable HCA in CSF. A similar relationship was found between Hcy and the other sulfur-containing EAAs CSA, HCSA, and CA.

CSF was also analyzed for eight other amino acids (aspartate, serine, glutamate, glutamine, glycine, threonine, arginine, and taurine) in a subset of the previous patients (Table 1). No significant differences between the treatment (n = 28) and control groups (n = 16) for aspartate, serine, glutamine, arginine, and taurine were detected by a two-tailed Mann-Whitney test. A significantly lower concentration of glutamate and significantly higher concentrations of glycine and threonine were detected by the two-tailed Mann-Whitney.

The CSF content of 5-methyltetrahydrofolate was compared for the treatment (n = 28) and control groups (n = 17). Although both groups had CSF folate levels in the normal range (40 to 80 nmol/L), we found that the treatment group had a lower concentration of folate (54.2 nmol/L ± 11.8) than the control group (82.8 nmol/L ± 9.0), which was demonstrated to be statistically significant ($P = .0245$) by a two-tailed Mann-Whitney test.

The control population is biochemically homogeneous. The control population was analyzed for differences between the patients with cancer and those with neurologic disease relative to the CSF concentrations of Hcy, HCA, CSA, HCSA, CA, folate, and the eight other amino acids. No significant differences were detected for Hcy (cancer 0.185 μmol/L ± 0.03 *v* neurologic disease 0.239 μmol/L ± 0.05), folate (cancer 75.5 nmol/L ± 13.1 *v* neurologic disease 83.3 nmol/L ± 11.8), or the eight other amino acids by a two-tailed Mann-Whitney test. With reference to HCA, CSA, HCSA, and CA, the two subgroups were identical.

One patient was excluded from the control group because she manifested significant baseline hyperhomocysteinemia of uncertain etiology. Her plasma Hcy level before antifolate therapy was 22.5 μmol/L (normal range, 1 to 10 μmol/L). This patient's CSF Hcy was also high (1.9 μmol/L), and HCA and CSA were present at 154 μmol/L and 36 μmol/L, respectively. HCA and CSA were detected in no other patients without prior antifolate therapy. Also excluded were two patients with dystonia who had received treatment with L-dihydroxy-phenylalanine (L-DOPA), which may cause an increase in Hcy. These two patients had CSF Hcy concentrations of 0.760 μmol/L and 0.930 μmol/L, but no detectable sulfur-containing EAAs.

Three patients manifested neurologic toxicity at the time of a scheduled lumbar puncture. Patient no. 1 developed seizures within 3 days of receiving oral MTX (25 mg/m^2 every 6 hours for four doses). Her CSF Hcy level, the highest recorded, was 3.862 μmol/L. Her HCA level was 126 μmol/L and her CSA level was 31 μmol/L. Patient no. 2 experienced an episode of ataxia, dysarthria, blurred vision, and confusion within 1 week of receiving intravenous MTX (2 g/m^2 over 2 hours). Her CSF Hcy concentration was 0.690 μmol/L; HCA and CSA levels were 269 μmol/L and 69.1 μmol/L, respectively, both of which were the third highest measured values. Patient no. 3 presented with a question of mild developmental delay at the time of diagnosis with acute lymphoblastic leukemia. During the course of his treatment, we noted marked neurodevelopmental regression, and computed tomography and magnetic resonance imaging of the cranium demonstrated evidence of mineralizing microangiopathy. Patient no. 3 received his last dose of MTX (25 mg/m^2 orally every 6 hours for four doses) 1 week before lumbar puncture, and his CSF Hcy level was 1.680 μmol/L. His CSF HCA and CSA concentrations were 416 μmol/L and 102 μmol/L, respectively, the highest measured for both compounds. In light of these findings, the intensity of this patient's systemic MTX therapy has been decreased, and he no longer receives intrathecal MTX.

Due to the small number of samples and several different regimens for systemic MTX (eg, 100 mg/m^2 as 25 mg/m^2 orally every 6 hours, and 2 g/m^2 intravenously over 4 hours), no correlation between CSF levels of the previous compounds and MTX dose was readily apparent.

DISCUSSION

Hcy is at a metabolic crossroads. It may enter the activated methyl cycle by remethylation to form methionine. Methylation is catalyzed by 5-methyltetrahydrofolate:Hcy methyltransferase, wherein 5-methyltetrahy-

drofolate serves as the methyl donor and cobalamin is a cofactor. This reaction provides the biochemical basis for the occurrence of hyperhomocysteinemia in folate and cobalamin deficiencies. Betaine:Hcy methyltransferase may also catalyze the methylation with betaine serving as the methyl donor. Alternatively, Hcy may enter the transsulfuration pathway by conjugation with serine to form cysteine. Hcy may also be oxidatively metabolized to HCA and HCSA.

Despite the identification of hyperhomocysteinemia as a risk factor for vascular disease and increasingly frequent monitoring of plasma Hcy levels, little is known about the presence of Hcy in CSF. Hyland and Bottiglieri[29] published a series of nine patients with motor neuron disease or peripheral neuropathy, but with normal serum B_{12} and RBC folate levels, in which the mean CSF Hcy concentration was 0.46 μmol/L (range, 0.28 to 0.66 μmol/L). Blom et al[34] analyzed CSF from six patients with neurologic disease not related to Hcy metabolism and found a range of 0.007 to 0.020 μmol/L for Hcy. Also reported by the latter group was a CSF Hcy concentration of 3.5 μmol/L for one patient with severe cobalamin deficiency and related neurologic disease. Similarly, Stabler et al[35] reported a range of 0.5 to 3.0 μmol/L for CSF Hcy in four patients with neurologic disease related to cobalamin deficiency. Finally, Bottiglieri[36] found that CSF Hcy ranged from 1.377 to 4.732 μmol/L in four B_{12}-deficient patients with subacute combine degeneration, and it was 0.493 μmol/L in one folate-deficient patient, with an adult control range (n = 18) of 0.015 to 0.140 μmol/L.

MTX can cause an initial biochemical, intracellular reduced folate deficiency, and ultimately an absolute deficiency.[37] Since folate deficiency causes a secondary elevation in Hcy, we determined the effect of MTX on CSF Hcy. We report here the largest series of CSF Hcy determinations published to date. We have shown that CSF Hcy in individuals not exposed to MTX is low, in accordance with previous few reports.[29,34-36] However, we found that MTX significantly raised the concentration of Hcy in CSF, and this effect may be sustained at least 1 week. Moreover, patients with neurologic toxicity had many of the highest measured values.

Elevation of plasma and CSF Hcy consequent to MTX administration may be important in the pathogenesis of MTX-associated neurotoxicity. Hcy is a highly reactive amino acid that is directly toxic to vascular endothelium, and exposure to it promotes a prothrombotic vascular endothelial surface.[16,17] Furthermore, hyperhomocysteinemia is a strong independent risk factor for vascular disease,[18] including stroke and carotid artery stenosis. The occurrence of focal neurologic deficits,[2-5] mineralizing microangiopathy,[19] and radiographic ischemic white matter changes[20] secondary to MTX therapy suggests that ischemic vascular disease may be involved. Hcy may be the mediator of this toxicity.

A related aspect of Hcy metabolism is also likely to be important in the pathogenesis of MTX neurotoxicity. EAAs, such as HCA and CSA, may be oxidatively derived from Hcy and cysteine, respectively. These compounds are putative neurotransmitters and are endogenous agonists of the NMDA receptor, a subtype of glutamate receptor.[21,22,24] HCA is known to accumulate in excess in patients with classic homocystinuria.[38] Similarly, rats made hyperhomocysteinemic by dietary Hcy supplementation will accumulate HCA.[39] CSA may also accumulate in states of Hcy excess that result from folate depletion due to shunting of Hcy through the transsulfuration pathway. Similar EAAs include HCSA and CA, closely related to HCA and CSA, respectively. EAAs are believed to be important in the pathogenesis of seizures[23-25] and it has been proposed that EAAs may be responsible for the seizures that occur in classic homocystinuria.[40] Furthermore, overexpression of EAAs may cause neuronal injury and death via excessive glutamate receptor activation. This mechanism of injury is called excitotoxicity and it has been implicated as a final common pathway for a wide range of chronic neurodegenerative disorders and acute neurologic processes, including stroke.[25]

The presence of HCA and CSA in whole brain tissue has been demonstrated[21,22,24]; however, little is known about their concentrations in CSF. We report here the first published series of HCA and CSA determinations in CSF. We have found that HCA and CSA are not detectable in the CSF of individuals without MTX exposure. However, we have shown that MTX markedly increased the concentration of these EAA neurotransmitters. Smaller elevations in the related compounds HCSA and CA were also observed, both of which were not detected in controls. Furthermore, all patients with neurologic toxicity at the time of lumbar puncture had marked elevations of HCA and CSA, and the patient with the highest measured values for both compounds presently suffers from severe chronic toxicity.

There appears to be two subsets of patients within the treatment group: those with and those without detectable HCA and CSA (Fig 2). However, it should be noted that all individuals without detectable sulfur-containing EAAs had CSF Hcy concentrations less than 0.355 μmol/L. Thus, there appears to be a threshold phenomenon for the appearance of HCA and CSA in the CSF. This observation implies that accumulation of these EAAs occurs only

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