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Substitutive Therapy in a Case of Methotrexate Neurotoxicity

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A SUBACUTE ENCEPHALOPATHY may develop within days or weeks in patients receiving intrathecal methotrexate (MTX) injections or after high-dose intravenous MTX therapy [1]. A transient defect in the metabolism of tetrahydrobiopterin (BH4; the required cofactor of hydroxylases for biogenic amines synthesis), leading to decreased availability of neurotransmitters, has been postulated as to be responsible for MTX neurotoxicity [2]. Such a mechanism is supported by the fact that, *in vitro*, MTX inhibits dihydropteridine reductase (DHPR), the enzyme required for the regeneration of BH4 from dihydrobiopterin (BH2). It has been suggested that substitutive therapy with neurotransmitter precursors and BH4 could prevent MTX toxicity. We report here a case of MTX neurotoxicity reversible under substitutive therapy which supports this hypothesis.

A 3-year-old boy was treated in February 1990 for bone marrow relapse of acute lymphoblastic leukaemia. Therapy consisted of weekly intravenous MTX over 1 h (80 mg/m^2 first week, 120 mg/m^2 second week and 160 mg/m^2 third week) with vincristine 1.5 mg/m^2 and asparaginase 20 000 U/m^2. Each course of MTX was followed by intrathecal administration of MTX 12 mg, cytarabine 40 mg. On 24 February, 2 days after completion of the third course, he became febrile and confused. Aphasia and increased tone of the limbs were noted. Cerebrospinal fluid (CSF) examination was normal. A few hours later, apyrexia was achieved but transient tremor of the limbs was observed. On 25 February, he became comatose and global hypotonia was noted. An EEG showed diffuse slowing and a cerebral computered tomographic (CT) scan revealed diffuse white matter hypodensity. 3 days later seizures occurred. The neopterin and total biopterin (BH4 + BH2) levels in CSF were, respectively, 28.7 nmol/l {normal: [mean (SD)] 19.4 (8.2)} and 14.8 nmol/l [normal: 24.6 (8.6)]. However, the proportion of BH4 was low. A treatment including intravenous leucovorin 100 mg/m^2/day and methylprednisolone 400 mg/m^2/day during 3 days was promptly administered. Because of the absence of clinical improvement, daily therapy with L-dopa 10 mg/kg, carbidopa 1 mg/kg and DL-5-hydroxy-tryptophan 7 mg/kg through a gastric feeding tube was started on 3 March. Improvement of neurological status was observed 2 days later with spontaneous ocular movements, coughing, deglutition and response to simple orders. Concurrently, the EEG returned to normal. On 6 March, oral administration of BH4 20 mg/kg was started. Spontaneous motility of the limbs was observed on 8 March, and he was able to swallow food. His language abilities returned slowly and neurological examination was normal on 17 March. The substitutive therapy was interrupted on 24 March. Neurological examination remained normal. 2 months later, the CT scan still showed areas of decreased attenuation. The patient presented a second medullar relapse and died in June 1990.

The clinical findings with demyelinisation at CT scan strongly implicate MTX as the aetiological agent of this sub-acute encephalopathy. A fall of BH4 levels in CSF is consistent with a DHPR inhibition. Such a biochemical profile is similar to that observed in rat pineal gland cultured in high concentration of MTX [3]. The therapy with L-dopa, carbidopa, 5-hydroxy-tryptophan and BH4 was based on the good results of such substitutive therapy in children with inherited biopterin deficiencies [4]. This successful treatment with neurotransmitter precursors and BH4 in a child with encephalopathy related to defect of BH4 synthesis following MTX therapy warrants confirmation by further observations.

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