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# PARAPLEGIA AFTER INTRATHECAL ADMINISTRATION OF METHOTREXATE*

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Methotrexate (MTX) has been widely used both orally and intramuscularly in the treatment of acute lymphoblastic leukemia (ALL) and in the field of oncology since 1948, after the discovery of aminopterin[1]. As a result of improved treatment which has led to long-term survival, relapses in the central nervous system (CNS) which were not seen in short-term cases are now being encountered. This has attracted attention to the intrathecal (IT) administration of MTX, which has been found to be the most effective method as regards both disease control and prevention of CNS involvement. As to the harmful side effects of this drug, the manifestations reported are, besides pain, sensorial deficit and sudden death[2], meningeal irritation phenomena[2-8], encephalopathy[9-13] and paresis[5,12] or paraplegia[5,7,14,17,18].

IT administration of MTX was first used in our clinic in 1975 for consolidation treatment. It has since been used as an agent for prophylaxis of CNS involvement. However, paraplegia having been observed in four of our patients in the last two years following IT administration of MTX, the subject attracted our attention. The aim of this paper is to present the findings of our experience on this subject, which is one that has already aroused interest in medical literature.

## Case Reports

### *Case 1*

E.D., a six-year-old boy, was diagnosed as having ALL on June 3, 1979, and he was treated weekly with vincristine (VCR) and daily with oral prednisolone (Pred). Complete remission was attained in six weeks. Thereafter he received consolidation

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(MTX 10 mg/$m^2$ intravenously (IV) for three days; cyclophosphamide (CYC) 600 mg/$m^2$ IV for two days; MTX 0.5 mg IT on the fifth day in a single dose) and maintenance therapy (6-mercaptopurine (6-MP) 2.5 mg/kg/day orally). At the beginning of the maintenance therapy, MTX (0.3 mg/kg/week, IT for five weeks) and cranial irradiation (3000 rad) were also applied for CNS prophylaxis. During the period of remission, reinduction therapy (Pred-VCR for two weeks and MTX IT in a single dose) was repeated every three months. Nine months after diagnosis and three weeks after the last IT MTX, the patient developed paraplegia, incontinence and encopresis. The cerebrospinal fluid (CSF) was normal except for a slight elevation of pressure. Suspecting medullary compression, antiedematous therapy and irradiation were applied to the area between cervical-3 ($C_3$) and sacral-2 ($S_2$) for one month. The paraplegia receded, but the patient still had bilateral steppage and a waddling gait. Testicular infiltration was later detected, treated and further remission obtained.

*Case 2*

A.Ş., a five-year-old boy, was diagnosed as having ALL on July 14, 1980, and systemic ALL therapy and CNS prophylaxis were given. In January 1982 he developed internal strabismus on the left and bilateral papilledema. Spinal fluid examination revealed elevated pressure, + + Pandy and 18 cells/$mm^3$. Because of the clinical findings, CNS involvement was suspected even though no pathological cells were found in the CSF. A week after IT administration of MTX paresis of the lower extremities developed, followed two weeks later by paraplegia. Bilateral mild papilledema was present. CSF was normal except for the increase in pressure and protein content. Electromyographic examination revealed that mild polyneuropathy was present. Paraplegia persisted.

*Case 3*

F.S., a five-year-old boy, was diagnosed as having Burkitt's lymphoma on September 25, 1980, through biopsy of a mass on the left side of the maxilla. Ziegler's drug schedule[15], which has to be repeated three times every other 2-3 weeks, was applied: CYC 1000 mg/$m^2$ IV and VCR 1.4 mg/$m^2$ IV on the first day; MTX 15 mg/$m^2$ IV on the second and third days and IT on the first and fourth days. The patient achieved complete remission. One week after the third course, the patient developed hyperesthesia, ascendant quadriplegia, incontinence, encopresis and dysphagia. CSF examination revealed increased pressure, + + + Pandy, normal sugar and chloride levels and a cell count of 27/$mm^3$ and no pathological cells. Eye fundi were normal. Polyneuropathical changes were found on electromyographical examination.

*Case 4*

A.Ç., a 44-month-old boy, had been diagnosed as having ALL in another hospital on August 13, 1980. A relapse occurred and he was admitted to our clinic on November 10, 1982. After two courses of a drug schedule consisting of daunorubicin, VCR and Pred had been given, remission was attained. Having had no CNS prophylaxis before his admission to our clinic, he was given weekly IT MTX and cranial irradiation. A week after the fifth IT MTX injection the patient developed flaccid paraplegia. CSF examination revealed an increase in pressure and protein content but no pathological cells. Polyneuropathic changes were detected on the electromyogram. Paraplegia persisted (Table I).

**Discussion**

Persistent paraplegia has been observed in three children with ALL and one with Burkitt's lymphoma after IT administration of MTX. Symptoms and signs started 1-3 weeks after administration . Two children were in remission, one had CNS infiltration and the one with Burkitt's lymphoma had no pathological findings during intrathecal MTX administration (Table I).

Incontinence and encopresis in two patients, loss of temperature sense in one and hypoesthesia in another accompanied the paraplegia. CSF examination revealed increased pressure and protein content in all patients whereas no increase in cell count was detected. Polyneuropathic changes were present on the electromyogram of three children, including the one with Burkitt's lymphoma. The paraplegia progressed to quadriplegia in one of the patients, regressed to steppage and a waddling gait in one and persisted in the other two.

In 1971, Baum *et al*[16] reported two cases of children with ALL in whom persistent paraplegia had been observed after prophylactic IT MTX administration. One of these developed quadriparesis while spastic paraplegia was observed in the second. Similar to this latter case, the waddling gait observed in one of our patients could be interpreted as spasticity. In a girl 12 years and 5 months old diagnosed as having lymphosarcoma cell leukemia, Luddy and Gilman[17] observed periumbilical pain after the fifth IT injection of MTX followed by flaccid paralysis and stool and urinary incontinence similar to our first two cases (Table II).

Persistent paraplegia concurrent with IT MTX administration has been observed during treatment of leukemic meningitis as well. For example, Back[2] reports the case of an 11-year-old child who had leukemic meningitis with pains in the left leg and abdomen after the third IT MTX injection. Although the injection was immediately discontinued an urticarial rash appeared on the legs, there was a sensorial deficit in the thoracic region, and the patient died of cardiac arrest. In such a case

TABLE I

**Paraplegia after Intrathecal Methotrexate (Cerrahpaşa)**

| Name | Age (years) | Sex | Diagnosis | No of MTX injections (IT) | IT dose (mg) | Time passed before beginning of symptoms (weeks) | Symptoms | Treatment | Prognosis |
|---|---|---|---|---|---|---|---|---|---|
| E.D. | 6 | M | ALL (remission) | 9 | 6.4 | 3 | Paraplegia, incontinence, encopresis, deep tendon R (−), LP: pressure. | Radiotherapy ($C_3$-$S_2$) + steroid + mannitol | Bilateral steppage and waddling gait |
| A.Ş. | 5 | M | ALL (meningeal) | 2 | 9 | 1 | Paraplegia, anesthesia, deep tendon R (−), EMG: polyneuropathy. | Steroid + mannitol | Paraplegia |
| F.S. | 5 | M | Burkitt's lymphoma | 5 | 9.3 | 1 | Quadriplegia, hyperesthesia, dysphagia, deep tendon R (−), EMG: polyneuropathy. | Steroid + mannitol | Quadriplegia |
| A.Ç. | 3 8/12 | M | ALL (remission) | 5 | 6.6 | 1 | Paraplegia, deep tendon R (−), EMG: polyneuropathy. | Steroid + mannitol | Paraplegia |

C: cervical; S: sacral; LP: lumbar puncture; EMG: electromyography

TABLE II

**Reported Cases of Paraplegia Following IT-administered MTX**

| Author | No. of cases | Age (years) | Sex | Diagnosis | Symptoms |
|---|---|---|---|---|---|
| Baum et al, 1971[16] | 1 | 6 | F | ALL | Quadriparesis 1 week after the 6th IT dose of MTX |
| | 1 | 8 | M | ALL | Paresis and spastic paraplegia after the 5th IT dose of MTX |
| Luddy and Gilman 1973[17] | 1 | 12 5/12 | F | Lymphosarcoma cell leukemia | Paraplegia and a sensory level at $T_4$ after the 5th IT dose of MTX |
| Gagliano and Costanzi, 1976[7] | 1 | 29 | F | CML (meningitis) | Paraplegia, neurogenic bladder after the 8th IT dose of MTX |
| Weiss and Kahn, 1978[18] | 1 | 46 | F | ALL (meningitis) | Flaccid paraplegia, sensory level at $D_{10}$, incontinence, encopresis, after the 5th IT MTX injection |

D: dorsal

acute arachnoiditis, one of the toxic side effects of MTX, should be considered, and because death was sudden it is rather difficult to talk of persistent paraplegia.

In a 29-year-old patient with chronic myeloid leukemia and leukemic meningitis, Gagliano and Costanzi[7] observed lumbar pain, atonic bladder and paraplegia six hours after an IT injection of MTX. In this case the toxicity of MTX was related to the presence of benzyl alcohol preservative. Six weeks later there was a partial recovery of the patient's motor functions. In the case of a 46-year-old woman with ALL who developed leukemic meningitis, Weiss and Kahn[18] observed progressive, permanent, flaccid paraplegia following MTX (paraben preserved) treatment and a rise in the CSF protein level during therapy (Table II).

Among 31 patients given IT MTX for leukemic meningitis Duttera *et al*[5] reported transient paresis in one, arachnoiditis in 17 and encephalopathy in two cases. However, they found no connection between these side effects and the preservative content of the MTX that had been administered. Moreover Naiman *et al*[3] also came to the conclusion that preservatives had no toxic effects. In eight children with ALL they observed chemical meningitis which began 2-4 hours after a prophylactic IT injection of MTX and which lasted for 12-24 hours. Mott *et al*[4] reported meningitis in a four-year-old boy during prophylactic treatment. Geiser *et al*[6] observed meningeal manifestations in 61% of 39 patients with ALL who were treated with prophylactic MTX and in 14% of 34 children receiving MTX concurrently with cranial irradiation. The authors have noted that the toxic clinical syndrome was reduced in patients receiving concomitant cranial radiation, probably due to the lympholytic effect of radiotherapy and the depressed cellular response of irradiated tissues.

Kay *et al*[9] report that seven patients developed encephalopathy after the IT administration of MTX. McIntosh and Aspnes[10] observed meningoencephalopathy in six of 33 children with ALL who had been given prophylactic treatment. Similarly Rubinstein *et al*[11] report 4 children with ALL and one with Burkitt's lymphoma who developed disseminated necrotizing leukoencephalopathy.

On computed tomography brain scanning of patients in whom MTX leukoencephalopathy developed, Peylan-Ramu *et al*[12] observed one or more abnormal findings in 53% of the patients. Dilatation of the ventricles, widening of the subarachnoid spaces, hypodense areas and intracerebral calcification were all detected. The absence of such conditions in the control group with ALL who had received no CNS prophylaxis, suggests the toxic effect of MTX[12].

The neurological effects of MTX can be grouped in the following three categories: paraplegia, arachnoiditis and encephalopathy. It has also been noted that paraplegia seen in the course of treatment of leukemic meningitis is more common in adults

than in children, which indicates a greater intolerance of MTX in adults. According to Ettinger *et al*[8], this is the result of a higher ratio of the volume of MTX administered to adults to the volume of their spinal fluid.

The toxic effects, in particular the persistent ones, of IT-administered MTX, which have been observed by us as well as by other authors and which have been noted in the literature review made by Kaplan and Wiernik[19], make it abundantly clear that the subject needs to be examined more closely. Nelson and Frank[20] stress the same point in their study on neurotoxicity. Although Ettinger *et al*'s[8] report of 1978, stating that no side effect is observed after IT administration of MTX in high doses, seems encouraging, the use of leucovorin, a folic acid derivative, together with this treatment is an obstruction to clear evaluation.

In the light of these findings and differing opinions, IT administration of MTX can be regarded as a rather hazardous procedure.

**Summary**

Four cases of paraplegia seen after intrathecal administration of MTX in three cases of acute lymphoblastic leukemia and one case of Burkitt's lymhoma are discussed, and cases from the literature are reviewed. Paraplegia developed one to three weeks after the administration of MTX. In addition to the paraplegia, two patients developed incontinence and encopresis, one anesthesia and another hyperesthesia. While some researchers relate the toxic effect of intrathecal MTX to its being administered with a preservative, others relate it to the patient's hypersensitivity or to the fact that it has been administered in conjunction with radiotherapy or intravenous MTX.

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