Methotrexate as a Corticosteroid-Sparing Agent in Complicated Neurocysticercosis

Edward Mitre, Kawsar R. Talaat, Michael R. Sperling, and Theodore E. Nash

Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences, and Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, and Department of Neurology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Background. A subset of patients with neurocysticercosis developed chronic or recurrent perilesional inflammation and required long-term and high-dose corticosteroid therapy. Such therapy frequently results in severe adverse effects. The purpose of this study was to determine whether methotrexate can be used as an effective corticosteroid-sparing or replacement agent in patients with complicated neurocysticercosis.

Methods. This study was a nonblinded, prospective, observational trial. Patients with neurocysticercosis who required prednisone (15 mg/day) or its equivalent for ≥2 months, were likely to require long-term corticosteroid therapy by nature of their disease, developed serious complications due to corticosteroid use, or presented with a long-term history of corticosteroid use and had continued evidence of ongoing inflammation were eligible for methotrexate treatment.

Results. Four patients are described in this study: 2 with subarachnoid neurocysticercosis, 1 with severe intraventricular and parenchymal disease, and 1 with recurrent perilesional edema around calcified lesions. Chronic inflammation due to neurocysticercosis resulted in lacunar infarcts, visual impairment, hydrocephalus, and seizures in these patients and necessitated long-term treatment with corticosteroids, which resulted in multiple adverse effects. The addition of methotrexate, prescribed at ≈20 mg/week, allowed for the successful reduction of corticosteroid use in all 4 patients and resulted in the improvement of many corticosteroid-associated adverse effects.

Conclusions. Methotrexate is a beneficial corticosteroid-sparing or replacement agent for patients with neurocysticercosis who develop chronic or recurrent perilesional inflammation.

Neurocysticercosis is caused by infection of the CNS with the larval form of the human tapeworm, Taenia solium. Clinical manifestations include seizures, headaches, and focal neurological deficits and are most often a result of cerebral inflammation that occurs in the context of degenerating or dead cysts [1]. Because of this, patients with neurocysticercosis are frequently administered corticosteroids to decrease the inflammation that normally occurs during the course of the disease or to decrease the anticipated perilesional inflammation that accompanies anthelmintic treatment [1]. Although there is significant morbidity associated with parenchymal neurocysticercosis, it can generally be effectively treated and usually requires only a short course of corticosteroids, if any, to attenuate symptoms that arise from perilesional inflammation around degenerating cysts [1–3].

Some patients, however, develop long-standing chronic or recurrent perilesional inflammation that can trigger recurrent seizures or focal neurological symptoms. This problem is most serious in patients with subarachnoid lesions in whom the parasite is often difficult to eliminate [4]. A significant cause of morbidity in areas of endemicity, relentless chronic inflammation associated with subarachnoid neurocysticercosis frequently occurs in untreated as well as treated patients and can result in lacunar infarcts, focal neurological deficits, and hydrocephalus [5]. Neurological complications also occur in a subset of patients with dead parasites who develop recurrent edema around parenchymal calcifications, possibly in response to sporadic release of retained parasite antigens [6]. Although not yet histologically proven, edema around calcifications likely represents inflammation and is associated with increased frequency of seizures [6–9].
Consequently, the most serious types of neurocysticercosis often require long-term and high-dose corticosteroid therapy. Such treatment can lead to severe and even life-threatening adverse effects [10]. Despite these risks, to our knowledge, there have been no clinical or experimental studies evaluating the efficacy of any corticosteroid-sparing drug therapy for patients with neurocysticercosis.

Recently, the use of high-dose and/or long-term corticosteroid treatment of complicated neurocysticercosis resulted in severe toxicities in several patients in our clinic that required consideration of alternative immunosuppressive medications. We opted to use methotrexate, because it is generally well tolerated at dosages of 25 mg/week and is well established as an efficacious corticosteroid-sparing or replacement therapy for a broad range of inflammatory disorders [11–14].

Previously, we reported the successful use of methotrexate as a corticosteroid-sparing agent in 1 patient with neurocysticercosis who experienced recurrent perilesional edema following treatment of large parenchymal cysts [15]. In this report, we describe 4 other patients with neurocysticercosis who have been administered methotrexate. Our results suggest that methotrexate is an effective and safe steroid-sparing or replacement medication for the treatment of complicated neurocysticercosis.

METHODS

Patients who required prednisone (15 mg/day) or its equivalent for 2 months, were likely to require long-term corticosteroid therapy by nature of their disease, developed serious complications due to corticosteroids, or presented with a long-term history of corticosteroid use and had continued evidence of ongoing inflammation were eligible for methotrexate treatment. Patients were observed frequently at the Clinical Center of the National Institutes of Health (Bethesda, MD) and by their own local physicians, when possible. Complete blood cell counts and liver enzyme panels were performed weekly for the first month, every other week for the next 2 months, and then every other month. Patients were monitored clinically for CNS signs and symptoms and underwent frequent MRIs to determine the degree and extent of perilesional enhancement and/or edema. All patients underwent regular neurological examinations, and those with visual symptoms had serial eye examinations by an ophthalmologist. Approved informed consent was obtained, and clinical research was conducted in accordance with guidelines for human experimentation, as specified by the Helsinki Declaration of 1975, and revised in 1983, by the US Department of Health and Human Services (Washington, DC). This study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board.

Four of 7 patients who received methotrexate are described below. Of the remainder, 1 patient was described previously [15], a second patient sought medical care elsewhere shortly after initiating therapy, and a third patient has only recently commenced methotrexate therapy and is still being evaluated.

REPORTS

Patient 1. Patient 1 was a 34-year-old Guatemalan man with subarachnoid neurocysticercosis. In 2002, he developed tingling in his left arm, perioral numbness, double vision, dizziness, headaches and intermittent vomiting. Neurological examination revealed mild, left upper extremity weakness; hyperactive reflexes that were brisker on the left side; and a left Babinski sign. MRI revealed diffuse leptomeningeal enhancement of the base of the brain, 2 cystic structures above the suprasellar cistern, mild hydrocephalus, and a single intracerebral punctuate calcification. Cysticercosis antibody was strongly positive, and in September 2002, after an episode of confusion and disorientation, he commenced a regimen of prednisone (40 mg/day) and was treated with an 8-day course of albendazole.

One day after finishing the course of albendazole, the patient experienced 2 episodes of confusion and incoherent speech. Additional MRI revealed a decrease in the size of the subarachnoid cysts and less enhancement in the subarachnoid spaces but new lacunar infarcts in the left globus pallidus and hypothalamus. The dosage of prednisone was increased to 60 mg/day and then tapered off by 19 October 2002. The following day, he developed a facial droop and collapsed as a result of weakness of the right lower extremity. MRI revealed new lacunar infarcts in the right putamen, right caudate, and left internal capsule. Prednisone therapy was restarted at 60 mg/day. On 28 October 2002, patient 1 developed vomiting and was prescribed dexamethasone (16 mg/day), in place of prednisone, and a 3-month course of albendazole.

Although patient 1’s symptoms improved, he developed severe complications associated with the use of corticosteroids, including Cushing syndrome, diabetes mellitus requiring insulin, depression, glaucoma, and proximal muscle weakness. Methotrexate treatment (7.5 mg/week) commenced on 23 January 2003, and the dose of corticosteroids was tapered very gradually over the next 6 months. Once corticosteroid therapy was finished, diabetes resolved, and the patient was able to discontinue insulin therapy. The MRI findings remained stable, with no further leptomeningeal enhancement, although mild communicating hydrocephalus persisted. The dosage of methotrexate was increased to 10 mg/week in February 2004 because lumbar puncture revealed mild CSF pleocytosis (28 WBCs/mL), as well as a persistently elevated protein level (95 mg/dL). During the same month, the patient developed bilateral aseptic necrosis of his hips, a likely complication of prolonged corticosteroid use, and required bilateral hip replacements. Patient 1 has been asymptomatic, with normal neurologic status, during the past 3 years of methotrexate therapy.

Patient 2. Patient 2 was a 44-year-old Honduran woman...
who presented in May 2001 with complaints of headache and blurry vision. MRI revealed inflammation of the optic chiasm and pituitary stalk in association with a complex ribbon-like cystic mass extending from the suprasellar cistern to the anterior arachnoid space along the pons and medulla. The combination of a single calcification in the right parietal region, subarachnoid cystic mass, and a positive cysticercosis serology established the diagnosis of subarachnoid neurocysticercosis.

Examination revealed bilateral papilledema and significant loss of visual fields bilaterally. Patient 2 was initially treated with albendazole for 4 months, resulting in the almost total resolution of the cystic mass. Although corticosteroids were able to control the inflammatory symptoms during and immediately following treatment with albendazole, the patient developed intolerable adverse effects including severe Cushing syndrome, myopathy, and diabetes.

During the first 19 months after treatment, we attempted corticosteroid tapering 8 times. During or shortly after each attempted taper, the patient developed severe headaches and/or worsening visual symptoms, such as the loss of visual fields (figure 1; months 0–19), likely associated with recurrent inflammation, because her visual acuity and visual fields rapidly improved after each administration of high-dose corticosteroids.

In December 2002 (figure 1; month 19), the patient commenced a regimen of methotrexate (10 mg/week) in addition to the corticosteroid regimen, which was tapered off by July 2003 (figure 1; month 26). Return of occipital headaches and renewed chiasmal enhancement prompted an increase in the dosage of methotrexate to 15 mg/week in September 2003 (figure 1; month 28), which resulted in clinical and radiological improvement. However, in late December 2003, while receiving 15 mg of methotrexate per week, the patient developed headaches, vomiting, eye pain, nuchal rigidity, decreased vision, and bilateral papilledema (figure 1; month 31). MRI documented a cystic mass in the suprasellar space, a new cystic mass at the junction between the medulla and pons, and an increase in lateral ventricle size. After the reintroduction of corticosteroid therapy and a further increase of the dosage of methotrexate to 20 mg/week, symptoms and signs quickly resolved. Because of suspected subarachnoid cysticercosis regrowth, patient 2 was administered a short 5-day course of high-dose praziquantel (100 mg/kg per day, in 3 divided doses), followed by an almost 3-month course of albendazole, which ended in late May 2004. MRI findings remained unchanged until March 2006, when a decrease in the size of the subarachnoid cysts was documented. Patient 2 has been asymptomatic since May 2004, with a maintenance regimen of 20 mg of methotrexate per week and 5 mg of prednisone every other day. In June 2006, she discontinued prednisone therapy, and since then, she has continued a regimen of 20 mg of methotrexate per week.

**Patient 3.** Patient 3 was a 32-year-old Peruvian woman who was healthy until October 2003, when she had 2 tonic-clonic seizures. MRI revealed multiple parenchymal cysts, including 1 with perilesional edema, 2 fourth ventricular cysts, 2 cysts in the left lateral ventricle, 1 degenerating cyst in the right lateral ventricle, and 2 cysts in the chiasmal region adjacent to the left and right middle cerebral arteries. Results of a Western blot assay for cysticercosis were positive. The patient was treated for 6 weeks with albendazole (400 mg twice per day) and dexamethasone (starting at 16 mg/day and weaned to 10 mg/day over the next 6 weeks).

Although the parenchymal cysts were degenerating, there was little change in the appearance of the ventricular and chiasmal cysts. High-dose praziquantel treatment with cimetidine was then administered for 2 months and resulted in some decrease in the size of the ventricular cysts and continued degeneration of the parenchymal cysts. Patient 3 developed a Cushingoid appearance and considerable weight gain while receiving high doses of corticosteroids. She started receiving a regimen of methotrexate (7.5 mg/week) in January 2004 in combination with a slow taper of dexamethasone. The patient was switched to prednisone in February 2004, after she completed the praziquantel regimen, and the dosage of methotrexate was increased to 10 mg/week. The corticosteroids continued to be tapered slowly over the next several weeks. While asymptomatic and receiving 10 mg of prednisone every other day, patient 3 developed mild hydrocephalus caused by obstruction of the fourth ventricle, which still contained 2 viable cysts. The dosage of prednisone was increased to 50 mg/day, and the fourth ventricular cysts were surgically removed without incident in March 2004. Corticosteroid treatment was discontinued in May 2004. In June 2004, the patient felt well, and MRI revealed no evidence of hydrocephalus. Although asymptomatic, an in-

![Figure 1. Temporal relation between initiation of methotrexate therapy, successful tapering of corticosteroid therapy, and decreases in episodes of visual loss (x) and severe headaches (O) in patient 2. All episodes of visual loss were confirmed by use of a computerized visual field analyzer.](https://academic.oup.com/cid/article-abstract/44/4/549/340127)
Figure 2. Axial fast fluid-attenuated inversion-recovery (FLAIR) MRI of patient 3 after removal of 2 fourth ventricle cysts in March 2004. Imaging on 4 June 2004 showed no evidence of hydrocephalus. Routine follow-up images taken 14 January 2005 showed significant hydrocephalus with increased transependymal flow of CSF by FLAIR MRI. Imaging on 22 April 2005, 3 months after the methotrexate dosage had been increased to 15 mg/week, revealed substantial reduction in both ventricular size and transependymal flow of CSF.

Figure 3. Temporal relation between initiation of methotrexate therapy, successful tapering of corticosteroid therapy, and decreases in MRI findings of perilesional edema (x) and clinical symptoms of seizures and focal neurologic deficits (◊) in patient 4.

DISCUSSION

In this report, we described the beneficial use of methotrexate as a corticosteroid-sparing agent in 4 cases of severe neurocysticercosis with chronic or recurrent cerebral inflammation. Patients 1 and 2 had subarachnoid neurocysticercosis and required long-term immunosuppression to prevent lacunar infarcts and visual impairment, respectively. Both patients developed significant adverse effects from corticosteroid treatment. The addition of methotrexate allowed for successful tapering of corticosteroid therapy in both patients. The use of methotrexate by patient 3 enabled stabilization and the partial reversal of hydrocephalus caused by chronic cysticercosis-driven inflammation, preventing the need for a ventriculoperitoneal shunt. Patient 4 has a long history of seizures in association with recurrent perilesional edema around calcified cysts. Since initiation of methotrexate therapy, her episodes of perilesional edema have ceased, and the frequency of seizures decreased in ventricular size was noted in January 2005 and was associated with significant periventricular enhancement by fast fluid-attenuated inversion-recovery (FLAIR) MRI (figure 2). Hydrocephalus was felt to be a result of ongoing inflammation in the subarachnoid space; and therefore, methotrexate was increased to 15 mg/week. MRI in April 2005 documented a decrease in ventricular size and a reduction in periventricular enhancement (figure 2). Mild enlargement of the ventricles was noted in July 2005, prompting an increase in the dosage of methotrexate to 20 mg/week. Since July 2005, the ventricular size has remained stable, and the patient has been clinically asymptomatic while receiving methotrexate at 20 mg/week.

Patient 4. Patient 4 was a 48-year-old woman with a history of cysticercosis dating from 1969 when she resided in India. Her history and clinical course were reported earlier until May 2001 [9]. She presented with seizures due to parenchymal cysts in 1969 that went undiagnosed until 1986, when she received a course of praziquantel. The parenchymal cysts resolved into about 55 calcified cysts. Patient 4 has been prospectively observed at the National Institutes of Health since October 1999. Nine episodes of seizures and/or focal neurological symptoms accompanied by 7 episodes of perilesional edema were documented from October 1999 through late February 2001 (figure 3; months 0–17) [9]. During the subsequent 3 months, she was successfully tapered off corticosteroid therapy and then experienced no symptoms for 13 months.

From June 2002 until January 2003, however, patient 4 experienced 5 clinical episodes of seizures and/or focal neurological symptoms, including at least 1 episode of status epilepticus, and multiple acute hospitalizations (figure 3; months 32–39). Although acute symptoms were controlled with corticosteroid therapy, symptoms and perilesional edema would recur during or shortly after tapering of corticosteroid treatment. To attempt to establish better control of the recurring perilesional edema, methotrexate (5 mg/week) was added to the corticosteroid treatment regimen in January 2003 (figure 3; month 39). Because of persistent perilesional edema and headache in February 2003, methotrexate was titrated to a dosage of 10 mg/week in March 2003 (figure 3; month 41). By the end of March 2003, the patient’s symptoms and MRI findings had improved, and she was able end corticosteroid therapy completely. The patient continued to receive 10 mg of methotrexate per week and was healthy until November 2005 (figure 3; month 73), when she developed seizures unaccompanied by perilesional edema. The dosage of her antiseizure medication had been decreased a few months earlier. The dosage of her antiseizure medications was readjusted, and the patient has remained asymptomatic through June 2006.
has markedly decreased in the absence of corticosteroid therapy. For all 4 patients, significant corticosteroid-sparing effects were obtained using $\leq$20mg of methotrexate per week.

In this study, all of the patients were given folic acid supplementation, because it has been shown to decrease the risks of chronic methotrexate therapy without significantly diminishing its beneficial anti-inflammatory effects [16, 17]. Although none of the patients in this report developed known methotrexate-related adverse effects, it is important to note that patient 2 developed probable regrowth of a portion of a subarachnoid cyst during methotrexate therapy. Although incomplete parasite eradication in response to anthelmintic therapy is well documented in subarachnoid neurocysticercosis [4], we cannot exclude the possibility that chronic methotrexate therapy in patient 2 prevented the patient’s immune system from completely killing the parasite. On the other hand, we also cannot exclude the possibility that methotrexate may have some cysticidal effect.

In conclusion, this report demonstrates that methotrexate can be a beneficial agent for the treatment of patients with neurocysticercosis with persistent or recurrent inflammation. At this time, we do not recommend methotrexate as first-line therapy to control inflammation in neurocysticercosis. The onset of action during methotrexate therapy is slow, and our experience is very limited. Furthermore, the majority of patients with neurocysticercosis only require a short course, if any, of corticosteroids to control inflammation induced by dying parasites. For patients with neurocysticercosis who develop chronic or recurrent cerebral inflammation, however, our experience suggests that methotrexate can be very beneficial as a corticosteroid-sparing or replacement agent.

Acknowledgments

Financial support. Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Potential conflicts of interest. All authors: no conflicts.

References