Effectiveness of Chloroquine and Hydroxychloroquine in Treating Selected Patients With Sarcoidosis With Neurological Involvement

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Objective: To assess the efficacy of chloroquine (Aralen) phosphate and hydroxychloroquine (Plaquenil) sulfate in the treatment of patients with neurosarcoidosis who either do not respond to corticosteroid therapy or develop unacceptable side effects.

Design: Retrospective study.

Setting: Sarcoidosis clinic at a university teaching hospital.

Patients: Twelve patients with biopsy-proved sarcoidosis, 6 women and 6 men ranging from 20 to 49 years of age, with neurological involvement.

Intervention: Chloroquine phosphate, 250 mg twice daily, or hydroxychloroquine sulfate, 200 mg twice daily, was administered for a period of 6 to 21 months. Patients had regular clinical evaluation, determination of serum and cerebrospinal fluid angiotensin-converting enzyme level, computed tomography or magnetic resonance imaging, chest radiography, lung function testing, and slit-lamp examination of the eyes.

Results: Chloroquine or hydroxychloroquine either stabilized symptoms or controlled neurological symptoms in 10 of 12 patients. Two patients failed to respond. Cerebrospinal fluid abnormalities, including lymphocytosis, were seen in 3 patients. Magnetic resonance imaging with gadolinium was most helpful in supporting the diagnosis of sarcoidosis and monitoring the course of the disease.

Conclusions: Chloroquine and hydroxychloroquine are effective in controlling neurological sarcoidosis in those patients who fail to respond to corticosteroids or develop severe side effects. Ocular toxic effects from chloroquine or hydroxychloroquine were not observed.

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Corticosteroids are the cornerstone of therapy for neurosarcoidosis. Although systemic corticosteroids suppress inflammation in many patients, the disease may require unacceptably high doses of the drugs to maintain improvement.1-3 In these patients, and in those in whom for other reasons corticosteroids may be contraindicated, methotrexate, azathioprine, cyclosporine, radiation, and other immunosuppressive drugs have been used.4-13 We report herein on our experience with the use of antimalarials—chloroquine (Aralen) phosphate and hydroxychloroquine (Plaquenil) sulfate—in 12 patients with neurosarcoidosis.

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RESULTS

Twelve patients, 6 women and 6 men from 20 to 49 years of age, formed the basis of this study. Seven were of African American origin. The chest x-ray film was abnormal in 10 (83%) of 12 patients; 6 had bilateral hilar adenopathy, 3 showed hilar adenopathy and pulmonary parenchymal involvement, and 1 patient had only pulmonary infiltrates. The diagnosis of sarcoidosis was based on the presence of noncaseating granulomas in the brain in 3 patients, in the lung in 5, in the lymph nodes in 2, in the nasal mucosa in 1, and in the skin in 1 patient. The Kveim-Siltzbach test was positive in the 1 patient in whom it was performed. Cerebrospinal fluid lymphocytosis and increased protein level were seen in 3 patients. Electromyographic changes consistent with axonal neuropathy were seen in 4 patients.

DIAGNOSIS

Magnetic resonance imaging with gadolinium enhancement showed characteristic abnormalities in 6 (67%) of 9 patients in whom it was performed (Table). In 10
PATIENTS AND METHODS

Between December 1965 and December 1995, 38 patients attending Los Angeles County–University of Southern California Medical Center and University of Southern California University Hospital, Los Angeles, were diagnosed as having neurosarcoidosis. These patients had clinical as well as histological evidence of multisystem sarcoidosis. Thirty-two (84%) of 38 patients received corticosteroids; 10 developed severe side effects, including depression, psychosis, suicide attempts (2 patients), uncontrolled hyperglycemia, unmanageable obesity, and severe osteoporosis. In these patients, corticosteroids were slowly reduced in dosage and then discontinued. At the same time, hydroxychloroquine sulfate, 200 mg twice daily, or chloroquine phosphate, 250 mg twice daily, was started and was continued for 6 months or more. Two additional patients, who did not wish to take corticosteroids, received hydroxychloroquine. All patients who received chloroquine or hydroxychloroquine had thorough eye examination, including a slit-lamp examination, at 3-month intervals by an ophthalmologist experienced in managing ocular sarcoidosis. Response to treatment was assessed by history, neurological and ocular examination, measurement of serum and cerebrospinal fluid (CSF) angiotensin-converting enzyme (ACE), computed tomography, magnetic resonance imaging (MR imaging), and gallium 67 (67Ga) scanning.

(83%) of 12 patients, chloroquine or hydroxychloroquine either controlled or stabilized neurological features. In 2 patients the disease progressed regardless of the type of therapy.

SIDE EFFECTS

One of the patients showed evidence of pigmented epithelial retinal deposits without any involvement of macula or fovea. Two had transient localized retro-orbital pain that subsided after discontinuing the drug. These 2 patients received a thorough examination including slit-lamp evaluation and MR imaging of the brain. No evidence of optic neuritis, papilledema, or retinal damage was observed. The pain did not return after the therapy was resumed. One patient (patient 4) developed bleaching of her hair.

SELECTED CASES

Case 1

In 1980, a 35-year-old man developed numbness of his left foot, pain in the left calf muscles associated with diminishing muscle strength, and difficulty walking. He paid little attention to his symptoms. In 1982, because of non-specific chest symptoms of tightness and cough, a chest x-ray film was obtained. It showed bilateral hilar adenopathy and pulmonary infiltration. A transbronchial lung biopsy showed noncaseating granulomas. Because he was not sufficiently symptomatic, he did not accept any treatment. In 1984, a repeated chest x-ray film and computed tomograms disclosed the changes seen in 1982. His chest tightness, cough, and symptoms of neuropa-thy were still present but not severe enough for the patient to accept therapy.

In 1993, his condition worsened and he agreed to receive treatment. He was given prednisone, 60 mg daily, with instructions to continue treatment for 6 months. After 2 weeks, the patient developed severe corticosteroid-induced side effects (psychosis, insomnia, memory loss, muscle weakness, and weight gain). He discontinued the drug and did not come for a follow-up visit until 1994.

At that time, he had been receiving no treatment for more than a year. His ataxia had worsened to the degree that he was nearly totally incapacitated. Neurological examination showed marked distal wasting of muscles, loss of touch and pain sensation over the hands and feet, and impairment of vibration sense distally. An electromyogram demonstrated severe, diffuse axonal loss, and sensorimotor neuropathy, involving sensory more than motor nerves and lower extremities more than upper extremities. The gradient distribution of abnormal findings in distal rather than proximal muscles was consistent with axonal polyneuropathy rather than mononeu-ritis multiplex. Magnetic resonance images of the brain, cervical spine, and thoracic spine and total-body gallium study were normal.

He was given chloroquine phosphate, 250 mg twice a day, for 6 months. He also received azathioprine, 150 mg daily, for 3 months. There was no response to either chloroquine or azathioprine. He was then given intravenous immunoglobulin (total dose, 2 g/kg of body weight) at monthly intervals for 3 consecutive courses. Subsequently, he received methotrexate, 20 mg orally, once a week for 3 months. No benefit occurred, and the patient’s condition continued to deteriorate.

Case 2

In January 1990, a 41-year-old woman developed distal weakness involving both arms and the left leg. There was some tingling associated with paresthesias. These symptoms lasted for about 2 weeks and slowly resolved. Three months later, left facial palsy appeared. Once again, she complained of vague muscle spasms and weakness of her left leg. Parotid glands were not enlarged. Other notable findings included left upper- and lower-limb weakness, clonus, right lid ptosis, and up-going toes on both sides. A chest x-ray film showed hilar adenopathy and pulmonary infiltrate. Examinations of the CSF originally showed no white blood cells, but progressed to show 16 lymphocytes on the second and fourth taps. The CSF protein level ranged between 0.41 and 0.63 g/L (41 and 63 mg/dL), with glucose of 3.0 mmol/L (54 mg/dL). Cultures of the CSF were negative for acid-fast bacilli and fungi. Results of serological studies including VDRL test, antinuclear antibody, anti–smooth muscle antibody, and anti–striated muscle antibody were normal. Serum ACE levels were 80 and 55 U/L on 2 occasions (reference range, 4-55 U/L). Magnetic resonance images of the brain and cervi-
cal, thoracic, and lumbar spine and bone scans were normal. Electroencephalograms showed attenuation of alpha rhythm and occasional theta activity.

Somatosensory evoked potentials of the left posterior tibial nerve were normal. Right posterior tibial nerve results were borderline normal, indicating a possible disturbance at the cortex. A transbronchial lung biopsy specimen showed noncaseating granulomas. An abnormal lung biopsy specimen, elevated ACE level, and CSF abnormality supported the diagnosis of neurosarcoidosis. The patient was given prednisone, 40 mg/d. She did not tolerate the drug and developed mood swings, acne, and weight gain. Chloroquine phosphate, 250 mg twice a day, was started and continued for 6 months.

When last seen in 1995, the patient was asymptomatic. There was no evidence of facial weakness. The weakness of the upper and lower extremities had subsided. She did not suffer from lower-leg numbing. Her chest x-ray film and ACE levels were normal.

**Case 4**

This previously healthy 36-year-old woman developed focal motor seizures and transient loss of control of the left leg. She had no fever, rash, tachycardia, or influenza-like syndrome before the episode. Although results of a neurological examination were normal, an MR image of the brain demonstrated an intracranial mass in the right hemisphere. A chest radiograph showed bilateral hilar adenopathy, and a $^{67}$Ga scan demonstrated uptake in hilar and parotid glands. The biopsy specimens of the brain mass showed noncaseating granulomas (Figure 1).

The patient’s condition responded to corticosteroids, but she developed severe psychological side effects and depression. The prednisone dosage was tapered and chloroquine phosphate, 250 mg twice a day, was added. Finally, prednisone was discontinued. The patient’s hair became bleached. Her condition remained stable for 2 years without seizures. At various times her medications included verapamil hydrochloride, sustained release (Calan SR), 120 mg twice a day; clonazepam (Klonopin), 0.5 mg, 1 mg every morning and noon, and 2 mg at bedtime for a total daily dose of 4 mg; paroxetine hydrochloride (Paxil), 30 mg before bedtime; the combination of isometheptine, dichloralphenazone, and acetaminophen (Midrin) for pain as needed; and sumatriptan succinate (Imitrex) 3 to 4 times a day. Her seizures recurred after the discontinuation of chloroquine, but continued to take the other medications for 12 months.
tion of chloroquine. Because 250-mg chloroquine phosphate tablets were unavailable, hydroxychloroquine sulfate was started at 250 mg twice a day. The patient became asymptomatic. This patient’s neurosarcoidosis was characterized by remissions and exacerbations. She will continue to need treatment for a long period.

Case 5
In 1983, a 33-year-old man of Dutch ancestry developed acute iritis, fever, erythema nodosum, and joint pains. About a year later he noticed weakness of the right hand grip. He could not twist caps off bottles with his right hand. Along with the progressive weakness, wasting of the right hand and forearm muscles became prominent. In early 1990, the patient began to have pain in the left forearm muscles, atrophy of the left thenar eminence, and numbness of the left thumb, index, and middle fingers. A chest radiograph showed diffuse pulmonary infiltrate. Noncaseating granulomas were present in lung biopsy specimens.

In June 1991, a neurological examination disclosed moderate atrophy of the right forearm and intrinsic hand muscles and selective atrophy of the left abductor pollicis brevis muscles. There were frequent twitches of the fingers on the right hand. Muscle strength was normal in the shoulders, upper arms, and wrist extensors. In the right arm, there was moderate weakness of wrist flexion and finger extension, slight weakness of hand grip, slight weakness of flexor pollicis longus and digitorum profundus, and severe weakness of intrinsic hand muscles. In the left upper extremity, strength was normal except for slight weakness of the abductor pollicis brevis. There was no weakness in the lower extremities. Reflexes were normal except for absent right finger flexion reflex, reduced left finger flexion reflex, and absent left ankle reflex. The plantar reflexes were flexor. Sensation was normal. Results of a nerve conduction study and electromyography were consistent with diffuse axonal neuropathy, predominantly motor, with some mild demyelinating features and relative preservation of the sensory potentials.

The patient was given prednisone, 60 mg/d, which he took for 3 months. His grip strength continued to deteriorate and was reduced to 8.1 kg. He also developed cognitive side effects. Corticosteroids were discontinued and chloroquine phosphate, 250 mg twice a day, was started. After 6 months his right hand grip improved and the left hand became almost normal. When the patient’s condition had stabilized, chloroquine was discontinued. In this patient chloroquine was effective despite the poor response to corticosteroids.

Case 6
In 1984, a 48-year-old man, otherwise asymptomatic, was found to have bilateral hilar adenopathy on a chest radiograph obtained during the workup for chronic sinusitis. Tuberculin, histoplasmin, and coccidioidin skin tests were negative. Serum ACE level was mildly elevated to 58 U/L (reference range, <52 U/L). In 1989, the patient became dyspneic. A chest radiograph at that time showed bilateral pulmonary infiltrates. A lymph node biopsy specimen showed noncaseating granulomas. Bronchial lavage failed to grow acid-fast bacilli or fungi. Lung function studies showed a vital capacity of 57%. Because of his symptoms, that patient was given prednisone, which he took for 6 months.

In January 1990, while not taking prednisone, he developed numbness of the right hand and tingling of
both hands and forearms. All upper-extremity muscle groups were mildly weak, with a score of 3 to 4 on a scale of 0 to 5. There was no muscle atrophy or fasciculation. An unenhanced MR image of the brain and spinal cord was normal in February 1990. An electromyogram and a nerve conduction study of the right upper extremity were normal except for mild slowing for motor median conduction across the wrist. The significance of the minimal stalling for median conduction was unclear. There was no evidence of radiculopathy.

Treatment was restarted with prednisone, 60 mg daily. Within 6 months, there was a complete resolution of numbness, tingling, and muscle weakness. The patient, however, had become severely depressed and cushingoid. The prednisone dosage was gradually reduced. When the dosage was reduced to 30 mg/d, his paresthesia reappeared and muscle weakness became prominent. He remained obese and depressed. A few months later his right Achilles tendon ruptured. At this point, hydroxychloroquine sulfate, 200 mg twice a day, was added. Prednisone was gradually reduced to 5 mg/d. His muscle weakness and numbness abated. Hydroxychloroquine was continued for 18 months. When last seen in 1995, the patient had no neurological symptoms. He had lost weight and was no longer depressed. A chest radiograph and serum ACE level were normal.

**Case 9**

A 47-year-old African American man with a history of pulmonary, cutaneous, and upper respiratory tract sarcoidosis, diagnosed in 1982, developed marked fatigue, headaches, and eye pain. Examination of his eyes disclosed mild low-grade vitreitis. Serum ACE level was normal. An MR image of the brain showed diffuse leptomeningeal enhancement in the frontal lobes, interhemispheric fissure, and right temporal and occipital lobes. There is no evidence of optic nerve involvement (patient 9; Table). Right, Much diminished leptomeningeal enhancement after treatment with hydroxychloroquine sulfate, 200 mg, twice a day for 5 months.

After 8 months his headaches and eye pain. Examination of his eyes disclosed mild low-grade vitreitis. Serum ACE level was normal. A chest radiograph and serum ACE level were normal.

**Case 11**

In March 1983, a 35-year-old African American man was examined because of increasing fatigue, polydipsia, nocturia, and decreased libido. A mediastinal lymph node biopsy showed noncaseating granuloma. A computed tomographic scan of the brain showed a 1-cm suprasellar enhancing mass. Serum ACE level was 69.0 U/L (reference range, 10-50 U/L). Prednisone, 40 mg/d, was started. In August 1983, computed tomography showed reduction in size of the pituitary mass. The patient did not tolerate prednisone; his weight and serum cholesterol level increased. Headaches reappeared and he developed uveitis. Optic atrophy secondary to a chiasmal mass appeared. This was most likely related to his poor compliance with treatment.

In 1988, an exploration of the optic chiasma was performed. The arachnoid at the base of the skull was peppered with sarcoid granulomas. The optic chiasma was diffusely thickened and enlarged. The lesion was not surgically resectable. Treatment was restarted with prednisone, 80 mg/d, which the patient did not take regularly. His neurological status deteriorated. His visual acuity was 20/200 OD and 20/80 OS. Because of the compliance problems and corticosteroid-induced side effects, the patient was given hydroxychloroquine sulfate, 200 mg twice a day. The patient’s condition stabilized initially, but the disease slowly progressed despite hydroxychloroquine therapy for 2 years. Regular neurological and eye examinations disclosed no evidence of hydroxychloroquine toxic effects.

**COMMENT**

Chloroquine phosphate, a 4-aminoquinoline, is used extensively in treating acute malaria. The anti-
inflammatory effects of chloroquine are well known. This drug has been used to treat rheumatoid arthritis, amblyopia, discoid lupus erythematosus, porphyria cutanea tarda, and solar urticaria. In recommended doses the drug is safe; however, in high doses it can cause irreversible ototoxic effects and retinopathy. The latter is related to drug accumulation in melanin-rich tissues.\textsuperscript{15,16} Prolonged treatment with chloroquine also can cause toxic myopathy, cardiopathy, and peripheral neuropathy and neuropsychiatric disturbances; all of these reactions improve if the drug is discontinued promptly.\textsuperscript{17,18} Both chloroquine and hydroxychloroquine should be used cautiously in the presence of hepatic or severe gastrointestinal tract disease, neurological disorders, and blood disorders. For patients receiving long-term high-dose therapy, ophthalmological and neurological evaluation is recommended every 3 to 6 months.

CHLOROQUINE WAS the first antimalarial drug to be used for controlling chronic cutaneous and pulmonary sarcoidosis.\textsuperscript{19,20} The only randomized double-blind clinical trial of chloroquine therapy for sarcoidosis was conducted by the British Tuberculosis Association in 1967; it reaffirmed the drug’s suppressive effect on sarcoidosis.\textsuperscript{21} Chloroquine also effectively reduces hypercalcemia of sarcoidosis.\textsuperscript{22} Chloroquine phosphate is given as a 250-mg tablet twice a day for 3 months and once a day for another 3 months. Ocular toxic effects are not seen with this regimen.\textsuperscript{23}

Hydroxychloroquine sulfate is a chloroquine derivative in which 1 of the N-ethyl groups is β-hydroxylated. Its therapeutic action against falciparum malaria is similar to that of chloroquine. It is preferred for treatment of rheumatoid arthritis, lupus erythematosus, and sarcoidosis because the ocular toxic effects are minimal.\textsuperscript{24} The dose is 200 to 400 mg/d. Ocular supervision is needed, although the drug has not been reported to cause retinal damage.\textsuperscript{25} Because hydroxychloroquine prevents insulin degradation in the liver, suppresses gluconeogenesis, and increases peripheral utilization of glucose, it is of particular value in patients with sarcoidosis with insulin-dependent diabetes who cannot tolerate corticosteroids and in those who develop unmanageable hyperglycemia because of corticosteroids.\textsuperscript{26}

The use of chloroquine or hydroxychloroquine specifically for neurosarcoidosis has not been described. In this small open trial with the use of these drugs in neurosarcoidosis, the following patterns emerged (Table).

1. The patients with neurosarcoidosis who failed to respond to corticosteroids did (case 5) or did not (cases 1 and 11) respond to chloroquine.
2. In patients who responded favorably to corticosteroids but did not want to continue because of severe corticosteroid-related side effects, chloroquine or hydroxychloroquine was beneficial in controlling the disease (cases 2 and 4).
3. For patients who could only tolerate smaller doses of prednisone because of side effects but whose disease required higher doses, adding chloroquine or hydroxychloroquine was desirable because of its corticosteroid-sparing effect (case 6).
4. In patients who did not wish to take corticosteroids, chloroquine or hydroxychloroquine could be given. In one such patient (case 9), there was clear evidence of improvement as evidenced on MR images. The second patient (case 10) showed only subjective improvement.

This was not a prospective, controlled, double-blind study. Furthermore, neither chloroquine nor hydroxychloroquine was compared with prednisone or any of the drugs used for treating sarcoidosis. Because of the limited experience with chloroquine or hydroxychloroquine in treating sarcoidosis, only vague clinical guidelines exist regarding the dose, duration of treatment, and need and means for monitoring drug toxic effects. In earlier years of this study, I used chloroquine phosphate, 250 mg twice daily, for 3 months followed by 250 mg once a day. The first course was almost always for 6 months. Complete eye examinations were performed at 3-month intervals. At the present time, chloroquine phosphate is available only in a 500-mg tablet size that is not tolerated well by patients because of gastrointestinal tract discomfort. I now use hydroxychloroquine sulfate exclusively in doses of 200 mg twice a day. Ocular examinations are conducted at 6-month intervals. The drug has been safely used for as long as 21 months continuously and more than 3 years on an intermittent basis.

Neurosarcoidosis presents a challenging problem as far as the diagnosis and monitoring of the disease are concerned. Although desirable, it is not always advisable or possible to perform a brain biopsy or obtain a neural specimen. Even if a biopsy specimen is secured, the random distribution of the granulomas may not always provide the firm diagnosis. In the present state of our knowledge, it appears that MR imaging may be the best objective measurement for monitoring therapeutic response of neurosarcoidosis to drug therapy. Six (67%) of 9 patients showed characteristic abnormalities, including pituitary and parenchymal masses, and hypothalamic, cerebral, and meningeal enhancement. Serial CSF examinations were used to assess the course in 3 of these patients.

Routine CSF examination disclosed mild and non-specific abnormalities; pleocytosis (31%-62%), increased protein content (50%-70%), and decreased glucose content (18%-31%). The CSF was normal in 30% or more of the patients, especially those with cranial and other peripheral nerve lesions.\textsuperscript{27} However, if present, CSF abnormalities may be used to monitor the course of sarcoidosis and its response to treatment. In this study, CSF ACE levels were not measured. Furthermore, serum and CSF ACE levels are of limited relevance because other neurological diseases including multiple sclerosis may have high ACE levels.\textsuperscript{28} The treatment of neurosarcoidosis remains unsatisfactory. Although corticosteroids are widely used, they are associated with substantial morbidity. Cyclosporine was found to be of benefit in at least three quarters of patients studied by Agbogu et al.\textsuperscript{29} Unfortunately, the relapse rate was high.\textsuperscript{29} Lower et al\textsuperscript{30} used methotrexate and cyclophosphamide in treating neurosarcoidosis. In their hands this type of chemotherapeu-
tic regimen has been associated with lower risk of ma-
ignant neoplasm, including bladder cancer. Radiation has
been used in refractory cases, but the response has been
eratic.

In conclusion, chloroquine and hydroxychloro-
quione are effective in controlling neurosarcoidosis. The
drugs may be beneficial in progressive inexorable dis-
ease unresponsive to corticosteroids. In the patients in
whom corticosteroids are clearly contraindicated, chlo-
roquine and hydroxychloroquine can play an important
role. Furthermore, in patients with marked side effects
of corticosteroids, particularly hyperglycemia, hydroxy-
chloroquine can be of use not only as a corticosteroid-
sparing agent but also as a blood glucose–lowering agent.

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