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Pilot Study of D-Penicillamine, Vitamins and Minerals in Multiple Sclerosis

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ABSTRACT

A pilot study of the effect of D-penicillamine in multiple sclerosis (MS) was undertaken because of D-penicillamine's activity against RNA neurotropic viruses,[1-4] because it is effective against the auto-immune disease, rheumatoid arthritis,[5-8] and because both viruses[9-19] and autoimmunity[17,20-22] have been implicated in multiple sclerosis. We have treated 16 patients with advanced MS, nine on full doses (2-2.25 grams/day) and seven whose treatment was permanently stopped for reasons other than adverse reactions. There has been some improvement in most of those whose treatment was not withdrawn, and no change or deterioration in those not continued on the therapeutic regimen. Despite use of a high dosage regimen, such as has evoked intolerable side effects in a high percentage of patients with rheumatoid arthritis,[23-25] we have experienced few side effects in a total of 48 patients suffering from diseases with auto-immune components, a finding we speculate is due to replacement of nutrients inactivated or removed by D-penicillamine, and to supplementation with selected nutrients.[26]

CASE REPORTS AND METHODS

Patients with advanced multiple sclerosis were treated with D-penicillamine in gradually increasing doses (250 mg initially, and increased by 250 mg daily increments at no less than one month intervals, as recommended for rheumatoid arthritis[7,8,24,25]), in combination with pyridoxine (150 mg/day) and zinc gluconate (45 mg Zn^{++}/day) divided in three daily doses (given at least one hour after the penicillamine) to compensate for their inactivation or removal by the drug.[27-29] We have also given higher than customary doses of SH-protective vitamins (1200 U. of E.; lower doses of B_1 and B_{12}) and of magnesium, when a deficit was demonstrable, as well as a high potency vitamin plus mineral supplement (Theragran M). This treatment plan had been formulated for the treatment of patients with Laennec's cirrhosis, who have multiple deficiencies and have had undetectable levels of vitamin E (Seelig et al, to be published), and was applied to patients with MS who also had low vitamin and magnesium levels. Of 16 patients with MS, all of whom were evaluated by objective parameters (utilizing grading of functions recommended in the Cooperative Study of Evaluation of Therapy of MS[30]) before treatment was started and at three to six month intervals in the course of therapy, six have received uninterrupted treatment with full dosage D-penicillamine (2-2.5 grams/day in four divided doses) for one to almost four years. Two had their treatment interrupted and then restarted, and eight had their treatment stopped for reasons other than adverse reactions.

Five of the six on uninterrupted therapy have improved by several objective parameters; in two the improvement has been dramatic. The most striking improvement is that of a 45 year old man whose MS had been progressive and unremitting for six years and who, when first seen by this group, had severely painful tonic spasms of all limbs, back, and neck and had lost half of his original weight (186 pounds). He was unable to move from a contorted fetal position. He had some diminution of tonic spasms and gained strength when D-penicillamine reached 750/mg day. The improvement did not persist at that dose, and dosage was gradually increased. He has been on treatment for three and a half years (2.25 g/day for a year), during which time he has regained his full weight, sits and goes about in a wheelchair, can transfer to and from his bed without aid, can stand and walk in parallel bars or with Canadian crutches, and has regained his ability to read and play chess. His initially abnormal EEG tracing is now normal. Another patient, a girl 30 years of age, had tonic spasms of her thighs when prevented even their forcible separation; she had lost all but slight peripheral vision, and was incontinent. She can now walk in parallel bars, has regained some vision and some bladder-control. Her intention tremor is better, and her mental clarity has improved sufficiently to permit her to resume writing poetry, a talent that had been lost for over two years. Her initially abnormal EEG is now normal. Notable, but less dramatic improvement has been seen in three additional patients on long-term uninterrupted therapy. A 44 year old man, with slowly progressive disease, has improved slightly in strength and skills; a 48 year old man, whose disease had exacerbated after a long remission shortly before treatment was begun, has

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stabilized and shown some improvement in strength and endurance. Neither had had abnormal EEG tracings at any time. A young woman of 35 years with severe cerebellar involvement has shown only slight improvement in her ataxia and tremor, no notable speech gains, but improvement in her electroencephalogram (EEG), after initial worsening. The sixth patient, a man of 30 years, on uninterrupted treatment, who also had severe cerebellar damage, showed temporary slight improvement (including the EEG), but then regressed both in ataxia and by EEG tracing. His treatment has recently been discontinued.

The ataxia of patients with cerebellar involvement has not responded as well to this treatment regimen as have other manifestations. Three of such patients have been on long-term therapy that has had to be interrupted: two when transferred to an acute facility for repair of fracture; one for tendon-release, when she suffered an exacerbation following severe psychological (familial) trauma. The latter 37 year old woman had been paraplegic for several years and was disoriented as to time and place on admission. She regained awareness of her surroundings, temporarily could stand with support and showed EEG improvement before she became cognizant of her personal difficulties, at which time her condition became much worse. One of the patients, a 59 year old woman who had had a cerebrovascular accident, as well as MS, whose therapy had been interrupted for hip surgery, had shown striking memory-improvement associated with an improved EEG and decreased tremor, all of which gains have been sustained on the low dosage (500 mg/day) D-penicillamine on which she has been maintained since her return to this hopsital. The third patient in this group, a 49 year old man, has shown no significant change, other than overall background improvement in the EEG; he has had more marked focal abnormality, however. All seven of those receiving D-penicillamine for prolonged periods, who had abnormal tracings, showed EEG improvement at some phase in their treatment. The improvement in all but one was sustained.

In contrast, none of the comparably ill seven patients whose penicillamine treatment had been permanently discontinued have shown any improvement. Two, who were stable when treatment was started, showed no change when it was stopped; their EEG tracings — normal at the outset — remained so. A 25 year old girl with respiratory difficulties when treatment was started accepted the treatment erratically, and died of progression of disease shortly after it was stopped. Two had to be terminated because sepsis developed that required treatment with toxic antibiotics, and did not have treatment restarted after cure of their systemic infections. Both subsequently showed marked deterioration, as did another patient whose acceptance of therapy had been erratic, and was discontinued for that reason. Two of these, who had repeated EEG tracings, showed further abnormality. Only one had been treated for over six months before being taken off the program (at parental request). She was a paraplegic girl of 27 years with large decubitus ulcers, recurrent complicating infections (before and while on treatment), intermittent retrobulbar neuritis, and mental deterioration. Her mental status and EEG improved while on therapy, but she suffered a severe sustained exacerbation and reversal of EEG improvement shortly after the penicillamine, but not the nutritional supplements, was stopped.

DISCUSSION

The efficacy of D-penicillamine in the auto-immune disease, rheumatoid arthritis,[5–8] and the evidence that auto-immunity contributes to demyelinating disease,[20–22,31,32] suggested its trial in MS. Perivascular lymphocytic "cuffing" has been described in brains of patients with neurological abnormalities,[31] and has been seen in experimental encephalomyelitis (EAE) and in MS,[32] to which EAE bears some resemblance.[20–22] Periarticular lymph nodes of patients with rheumatoid arthritis have been shown to produce rheumatoid factor;[33,34] periarticular lymphoid nodules of patients with rheumatoid arthritis have disappeared as the patients responded to D-penicillamine.[35] Vasculitis of rheumatoid arthritis has also responded to treatment with D-penicillamine,[6,7] and a child with progressive systemic sclerosis and vasculitis with perivascular lymphocytes, also showed improvement of her muscle and skin lesions with D-penicillamine therapy.[36] It was reasoned that the perivascular lymphocytes of MS might similarly reflect local autoimmune activity that might respond to D-Penicillamine.

In addition, the drug has anti-viral activity against neurotropic viruses such as poliovirus[1–4] and Coxsackie and Forest-Semliki viruses (personal communication, Squibb Institute for Medical Research). Thus, evidence that viral infections are implicated in several animal and human demyelinating diseases, including MS (review[15]), further justified a therapeutic trial in MS. It has been postulated that infection-altered nerve tissue might be antigenic, both in EAE and MS.[16,21] It is considered likely that the neuro-antigen is derived from virus-damaged nervous tissue and that MS is an infection caused by a slow virus with a long latent period.[9,15–17,22] Electron microscopic demonstration and culture of nucleocapsids of paramyxovirus in brain tissue of patients who died with active MS,[10–14,18] and immunofluorescent demonstration of measles virus in the jejunal mucosa of MS patients[19] provide the most convincing evidence of viral involvement in this disease.

One surprising finding deserves note. In the course of monitoring our patients to detect anticipated thrombocytopenia (a reported side effect of D-penicillamine[23]) we found that all of the MS patients on sustained treatment occasionally showed increased platelet counts (usually coincidentally with or antece-

dent to clinical signs of improvement), from previously low counts. Platelet counts as high as 500,000 have occasionally been seen in most of our MS patients on treatment. This recalls the evidence that, during MS-exacerbation, there can be a fall in platelet counts with a rise occurring during improvement.[37] Perhaps the observed rise in platelet counts may prove an objective index of improvement. It is reminiscent of the suggestion that formation of microthrombi participates in the pathogenesis of MS.[38] Whether D-penicillamine inactivates or prevents synthesis of a serum factor that increases platelet adhesiveness in the active phase of MS[39] requires further study.

We have encountered few side effects in patients on D-penicillamine among our total of 48 patients,[26] only five of which might have been related to the drug since they subsided when treatment was stopped: a faint rash, proteinuria (in a patient with a history of penicillin anaphylaxis) and transient hematuria in a cirrhotic patient while on and off therapy. This patient refused a renal biopsy and has not been rechallenged. Before we added zinc to the regimen, one patient (with chronic active liver disease) lost his sense of taste, which was promptly restored on zinc supplementation. Another with cirrhosis of the liver developed ecchymosis on high dosage. This is in contrast to the incidence of acute and late (serious) adverse side effects that has necessitated discontinuation of D-penicillamine therapy in more than a third of rheumatoid arthritis patients.[8,23–25] It is possible that administration of pyridoxine (which D-penicillamine inactivates by forming a thiazolidine derivative[27]) and of zinc (which is chelated by D-penicillamine[40]) might have contributed to our patients' tolerance of the high dosage regimen. We speculate that use of sulfhydryl (SH)-protective vitamins might also have been useful, since some of D-penicillamine's therapeutic effects in intermediary metabolism (in Wilson's disease) have been attributed to its SH-radical.[41] Furthermore, of nine MS patients whose vitamin E blood levels were measured before starting the program, seven had lower than normal levels (0.2-0.7 mg%; normal range=0.8-1.2); and one was marginally low (0.9). Thus SH-protective vitamins, such as vitamin E,[42,43] B_{12},[44,45] and C,[43] were included in the regimen.

CONCLUDING COMMENTS

Our use of high doses of D-penicillamine in MS and other conditions with auto-immune components was predicated on the observation that most of our patients did not begin to show improvement, or did not sustain it, until the high dosage level had been reached. In the early phase of our study, the prompt response of three patients, two with cirrhosis and one with MS (while on 500-750 mg/day), led us to continue those low doses for several months, increasing dosage only on evidence of further advancing disease or cessation of improvement. Subsequently, we have followed a monthly 250 mg/day increment-program with most of our patients. The low incidence of side effects might possibly be the result of the nutritional supplements. Remaining to be explored is whether patients in earlier stages of MS might respond to the low doses of D-penicillamine that are under investigation, in an effort to reduce the incidence of adverse reactions in active rheumatoid arthritis[25] (p.c., I.A. Jaffe). The naturally remitting course of MS does not permit assurance that the improvement that we have seen in most of those on long-term treatment is necessarily a response to our therapeutic regimen. The contrast between those on sustained therapy and those whose treatment was stopped, however, is hopeful. Arrangements are being made for a double-blind study of patients with earlier forms of the disease, to test the anecdotal findings reported here.

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