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Short Report

EFFECT OF A SYNTHETIC POLYPEPTIDE (COP 1) ON PATIENTS WITH MULTIPLE SCLEROSIS AND WITH ACUTE DISSEMINATED ENCEPHALOMYELITIS

Preliminary Report

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SUMMARY

Three patients with acute disseminated encephalomyelitis (ADE) and 4 patients in the terminal stages of multiple sclerosis (MS) were subjected to treatment with Cop 1, a synthetic copolymer of amino acids, which had previously been shown to have a beneficial effect in the treatment of experimental allergic encephalomyelitis (EAE). Under the treatment, the ADE patients recovered completely within 3 weeks, but 1 of 2 control cases treated with steroids showed complete recovery as well. The MS patients did not show any significant change in their motor function; however, 2 of them showed some improvement in vision and speech capacity. It is too early to conclude whether this improvement is related to the treatment. No side effect was observed in any of the patients treated with Cop. 1.

INTRODUCTION

Previous studies from our laboratory have demonstrated that a synthetic basic copolymer of amino acids, denoted Cop 1, is effective in the suppression of experimental allergic encephalomyelitis (EAE) (Teitelbaum, Meshorer, Hirshfeld, Arnon and Sela 1971; Teitelbaum, Webb, Meshorer, Arnon and Sela 1972; Teitelbaum, Webb, Bree, Meshorer, Arnon and Sela 1974). EAE is a neurological autoimmune disease induced in laboratory animals by a single injection, in complete Freund's adjuvant

(CFA), of brain or spinal cord tissue, or the myelin basic encephalitogenic protein (BE) isolated therefrom (reviewed by Paterson 1966). The disease was shown to be the result of a cell-mediated immune response to the BE, and can be specifically prevented or suppressed by appropriate treatment with BE or several fragments and derivatives of it (Shaw, Alvord, Fahlberg and Kies 1962; Einstein, Chao and Csejtey 1972; Swanborg 1975). As mentioned above, the synthetic copolymer Cop 1, which is immunologically cross-reactive at a cellular level with BE (Webb, Teitelbaum, Arnon and Sela 1973), could also decrease both the incidence and severity of EAE (Teitelbaum et al., 1971). In view of this specific suppressive activity it was of interest to find out whether Cop 1 might have any effect on demyelinating diseases in humans which are in some ways comparable to EAE, such as acute disseminated postinfectious encephalomyelitis (ADE) or multiple sclerosis (MS).

ADE is similar to EAE in its clinical course, pathological manifestations and immunological features (Paterson 1971; Lisak, Behan, Zweiman and Shetty 1974); hence, EAE is its true model in experimental animals. Multiple sclerosis is a more complex disease, with no parallel in animals. EAE, although not exactly similar, but rather differing from it in several aspects, is still the only relevant experimental disease which resembles MS, and therefore serves as a putative experimental model for it (Paterson 1971).

In view of this possible relationship between these two human diseases and EAE, we carried out a limited clinical trial in several patients with ADE and MS, to find out the potential effect of Cop 1.

MATERIALS AND METHODS

Materials. BE was purified from bovine spinal cord according to the method described previously (Hirshfeld, Teitelbaum, Arnon and Sela 1970). Cop 1 was the material described in our earlier publication (Teitelbaum et al 1971).

Methods. Skin tests with both BE and Cop 1 were performed by intradermal injection of 10 μg in physiological saline. A lymphocyte stimulation test was carried out on peripheral blood lymphocytes as described previously (Webb, Teitelbaum, Abramsky, Arnon and Sela 1974). Biochemical, hematological and serological tests on blood, urine and cerebrospinal fluid (CSF) samples were carried out under routine conditions in the clinical laboratories of the Hadassah University Hospital. The level of gammaglobulin in the CSF was determined by electrophoresis on cellulose acetate, followed by staining with Nigrosine.

PATIENTS

(A) ADE patients

Two of the ADE patients (aged 14 and 12 years) had developed convulsions with pyramidal signs, or coma, respectively, 1–2 weeks after recovering from measles. A third ADE patient had post-mumps optic neuritis, with mild signs of encephalitis. The electroencephalogram (EEG) was diffusely disturbed and CSF examination revealed

pleocytosis and a high level of protein in all cases. All 3 patients gave positive skin tests (> 5 mm) with BE and were negative with Cop 1 before treatment.

(B) MS patients

The criteria for the diagnosis of MS were those described by McAlpine (1972) in patients with characteristic histories of relapse and remission and evidence for multiple lesions. The individual patients are described in the following:

Case 1. The first of 4 patients, B. T., a 40-year-old man, suffered from MS for 8 years. Before the initiation of trial he was bedridden, and had a spastic paraparesis, moderate optic neuropathy and severe cerebellar disturbances. The course of his disease in the last 2 years had shown constant and progressive deterioration, with 8–9 relapses per year.

Case 2. The second patient, J. S., a 23-year-old man, had suffered for 3 years from a fulminant non-remittent form of MS. He was paralyzed in both legs and arms and had severe cerebellar, ocular and bulbar dysfunction. He was unable to eat or talk and was fed by stomach tube. He already suffered from pressure sores when treatment was initiated.

Case 3. The third patient, A. M., a 30-year-old woman, had had MS for 2 years. She had weakness in her legs and showed very serious incoordination of her limbs. She also had disturbances of vision and dysarthria of cerebellar type.

Case 4. The fourth patient, S. C., a 40-year-old woman had suffered from MS for over 10 years, and was in a relatively static phase of the disease, with sporadic relapses and remissions. At the beginning of the treatment, she had weakness in her legs and was confined to a wheelchair.

Treatment with Cop 1. Cop 1 was administered intramuscularly in an aqueous solution in physiological saline. The ADE patients received daily injections of 2 mg Cop 1 for 2 weeks. The MS patients received a course of initial treatment, while hospitalized, consisting of a series of injections of 2–3 mg of Cop 1 every 2–3 days for 3 weeks. In the second stage of the treatment, which was not during hospitalization, each patient received a weekly injection of 2–3 mg over 2–5 additional months.

RESULTS

All 3 ADE patients showed a complete recovery within 3 weeks from the initiation of treatment. Out of 2 other ADE patients who did not receive Cop 1 but were treated with steroids, 1 recovered completely, whereas the second patient recovered from the acute phase of the disease, but retained part of the neurological symptoms during a long period thereafter.

The results with the MS patients are summarized in Table 1. The clinical condition of 3 cases (Cases 2, 3, 4) remained static during the treatment period and, although no improvement was observed, there was no further deterioration in their motor function. Case 3 and to a lesser extent, Case 2, showed mild to moderate improvement in speech and visual function. The first patient showed initial remission for 3 months, but thereafter suffered a relapse while still under Cop 1 treatment.

No side effects were noted in any of these patients. There were no changes in the blood pressure, heart rate and electrocardiogram (ECG). No allergic reactions were observed and no clinical toxic reactions were noted. Blood count, urine and blood tests which included biochemical analysis and tests for liver and kidney function all remained completely normal throughout treatment.

TABLE 1

COP 1 TREATMENT IN MULTIPLE SCLEROSIS

Case No.	Duration of treatment	γ-Globulins in CSF (%)	Lymphocyte transformation (SI)[a]		Clinical changes observed
			BE	Cop 1	
1	3 months	17.1 → 7.3 → 14.5	1.3 → 2.7	1.2 → 2.4 → 1.5	Initial remission for 3 months and then relapse
2	6 months	23.0 → 23.8	1.9 → 2.9 → 1.2	1.0 → 1.7	static (following rapid deterioration before treatment)
3	4 months	16.9 → 13.2	0.8 → 2.6	0.9 → 2.2 → 1.5	improvement in speech and vision. No change in motor functions
4	6 months	17.4 → 17.0	1.5 → 1.0	3.5 → 6.8 → 2.5	static

[a] The values represent the stimulation indices of incorporation of [^{3}H]thymidine by the cells.

There was no change in the immunoglobulin levels in the blood, which were normal. The levels of immunoglobulins in the CSF decreased in 1 patient (Case 1) from 15.9% to a normal value of 7.0% of the total protein; a smaller reduction was observed in another patient (Case 3), and in the others the level remained unchanged. The cellular immune response to BE and Cop 1 during the treatment was evaluated by the in vivo skin test and the in vitro lymphocyte transformation test using peripheral blood lymphocytes. Skin tests for both BE and Cop 1 were negative before treatment and during the first 3 weeks of treatment. As seen in Table 1, there was usually a gradual increase in the in vitro response to Cop 1; the response to BE which was negative in all patients at the beginning became positive in 3 cases.

DISCUSSION

The involvement of immune processes in MS, and specifically autoimmune reactions, has prompted immunological approaches to the study of the disease mechanism and possible treatment of MS. There are two main alternative approaches to immunotherapy in this case: (a) general suppression of the immune mechanisms by either anti-lymphocyte serum or immunosuppressive drugs and (b) administration of appropriate antigen(s) for specific suppression of the relevant immune response — a process which is comparable to desensitization in allergic disorders.

Attempts have been made using both of these approaches. Thus a recent publication reported successful results obtaining relief in several MS patients by the drastic combined use of several forms of immunosuppressive treatment, namely, anti-lymphocyte globulin, thoracic-duct drainage, together with azathioprine and steroids (Ring, Lob, Angstwurum, Brass, Backmund, Seifert, Coulin, Frick, Mertin and Brendel 1974). In addition several medical groups have attempted to treat MS patients only with steroids (Rose, Kuzma, Kurtzke, Namerow, Sibley and Tourtellotte 1970), or

with immunosuppressive agents such as azathioprine (Silberberg, Lisak and Zweiman 1973), or antilymphocyte serum (MacFadyen, Reeve, Bratty and Thomas 1973), with limited success. The application of specific desensitization was reported by Campbell, Vogel, Fisher and Lorenz (1973) in a clinical trial using human BE as the desensitizing agent.

The present report was based on the resemblance between MS and EAE, using synthetic Cop 1 which has a suppressive effect on EAE. Indeed Cop 1 did seem to have a positive influence in ADE, which is the human disease which most closely resembles EAE, although the small number of cases does not permit definite conclusion to be drawn. The possibility that the apparent improvement under Cop 1 treatment could have occurred spontaneously cannot be excluded, and only an extended study will give an answer to this question. Clinical study of ADE patients is of importance in view of the observation that among ADE patients some eventually prove to have MS (Lumsden 1970). Another possible linkage between ADE and MS is the presence of lymphocytes sensitized to BE in most ADE patients (Lisak et al. 1974) and in a proportion of MS patients (Webb et al. 1974; Sheremata, Cosgrove and Eylar 1974).

With regard to the results in the MS patients, from the trial reported in the present study it is difficult to draw clear-cut conclusions for several reasons: first, the number of patients was very small and second, all of them were terminal patients, namely, in a *very* advanced stage of the disease, in whom the damage to the nervous system could have been irreversible. In these patients we did not observe any improvement in motor function, but 2 of them showed some improvement in vision and speech which could have been the direct result of the Cop 1 treatment, although the effect might have been a part of the short-term clinical variation which is known to be common in MS.

One of the important observations of this study is that treatment with Cop 1 did not result in any side effects in the patients, nor did it cause any toxic or allergic reactions. Furthermore, recent experiments show that it has no toxic effect either in mice, rats, rabbits and dogs. These findings, in addition to the fact that Cop 1 has no general immunosuppressive activity (Teitelbaum et al. 1972), renders this treatment suitable for further clinical trial. In future trials it may be preferable to use Cop 1 or BE in those MS patients who show, before treatment, cellular sensitivity to BE, and who may thus be more suitable candidates (resembling the situation in EAE and ADE). In any such treatment Cop 1 may have some advantage over BE, since it is completely non-encephalitogenic.

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