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SHORT REPORTS

Topical treatment of recurrent cutaneous leishmaniasis with ointment containing paromomycin and methylbenzethonium chloride

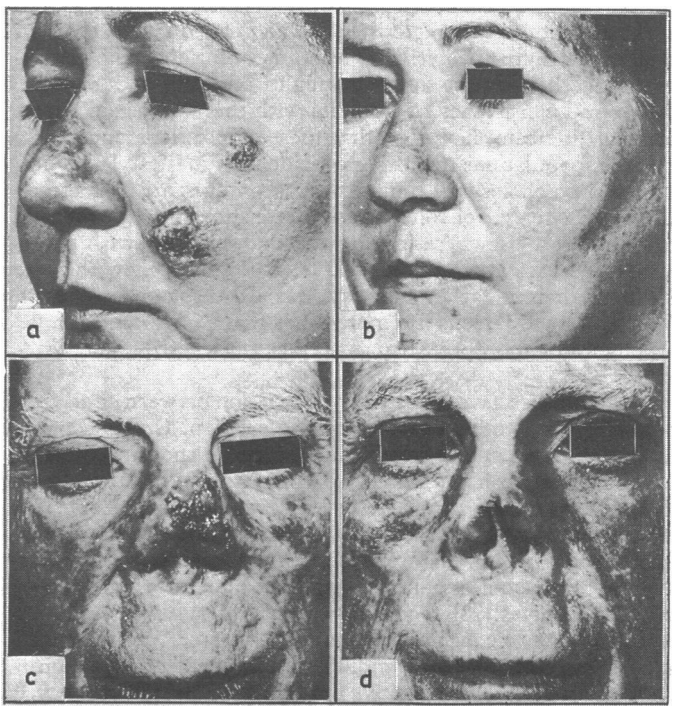
Cutaneous leishmaniasis, a protozoal disease, continues to present important therapeutic problems and, though usually self limiting, can cause considerable morbidity. It may result in severe disfigurement. Recurrent cutaneous leishmaniasis, or leishmaniasis recidivans, is a rare form of the disease caused by *Leishmania tropica* (formerly *L tropica minor*), and occurs on or near healed leishmaniasis scars months to years after total or partial resolution of the acute lesion.

Currently, no satisfactory treatment exists for either condition. The available drugs—the pentavalent antimonials, the diamidines, amphotericin B, and emetine hydrochloride—are all unpredictable and unsatisfactory and occasionally cause severe toxicity.[1] Few studies have dealt with topical treatment. Recently, local treatment with chlorpromazine ointment was successfully used against diffuse cutaneous leishmaniasis.[2] Topical treatment with imidazole derivatives, however, was ineffective in cutaneous leishmaniasis in both experimental animals and man.[3]

During the past few years an effective topical treatment of cutaneous leishmaniasis has been developed. BALB/c mice with early and advanced infection with *L major* LRC-L137 were treated with an ointment containing 15% paromomycin sulphate and 12% methylbenzethonium chloride in white soft paraffin (UK patent number GB 2117237A). All the mice were completely cured of cutaneous disease after application of the ointment twice daily for six to 10 days.[4] Treatment of lesions in the base of the tail eliminated only the parasites in those lesions; the internal organs and other, untreated lesions remained heavily infected.

Case reports

In a preliminary clinical study two patients with recurrent cutaneous leishmaniasis were treated with an ointment comprising 15% paromomycin sulphate and 1% methylbenzethonium chloride (supplied by Teva Pharmaceutical Industries Ltd, Jerusalem) twice daily for 80 days.



Effect of treatment on recurrent cutaneous leishmaniasis. Case 1: (*a*) before treatment; (*b*) four months after end of treatment; Case 2: (*c*) before treatment; (*d*) one month after end of treatment.

Case 1—The patient was a 54 year old woman with a 50 year history of leishmaniasis who had immigrated from Iraq in 1951. She had three crusted, ulcerated lesions 1-3 cm in diameter, one on the nose and two on her left cheek (figure (*a*)). Before attending our clinic she had been treated unsuccessfully with emetine hydrochloride, with severe toxic side effects.

Case 2—The patient was a 58 year old man with recurrent cutaneous leishmaniasis, which had first developed 47 years previously, also in Iraq. He had been unsuccessfully treated with various drugs including emetine

hydrochloride given alone and with steroids.[5] He had one ulcerative, exudative lesion 4 cm in diameter located on the nose (figure (*c*)).

Parasites isolated from the lesions of both patients were cultivated on blood agar medium and identified, by serological examination and isoenzyme analysis using thin layer starch gel electrophoresis, as *L tropica* of serotype A_2, the aetiological agent of recurrent cutaneous leishmaniasis.

In case 1 the parasites were eliminated from the lesions on the nose and upper portion of the cheek after 45 days of treatment but were still present in the lesion on the lower portion of the cheek. Another 20 days' treatment improved the lesion clinically, and an additional 20 days' treatment were required to eliminate the parasites totally. Healing was complete within three to four weeks after the end of treatment, with negligible scar formation on one lesion and good cosmetic results on the two others (figure (*b*)). The patient was observed for 12 months after the completion of treatment, during which time no relapse or any symptom of the disease occurred. The lesions were completely healed, and biopsy specimens were free of parasites.

During the first seven days of treatment in case 2 the lesion improved clinically but living parasites were still present. The patient was treated for an additional 73 days, after which time the parasites were completely eliminated and the lesion healed (figure (*d*)).

The treatment was well tolerated, and no adverse clinical or laboratory side effects occurred.

Comment

Although the present study covered only 10-12 months of observation this treatment appears to be superior to the other available regimens because it is simple and does not cause discomfort or side effects.

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Nutritional support improves antibody response to influenza virus vaccine in the elderly

Recent studies have confirmed that protein-energy malnutrition and deficiencies of several nutrients result in impaired immune responses, particularly cell mediated immunity.[1] In old age there is a progressive decline in immunological vigour,[2] and old people also show alterations in dietary intake, catabolism, and needs, with consequent changes in nutritional state and body composition. Many people over 65 have obvious or subclinical nutritional deficiencies.[3] We have observed that correction of nutritional deficits and imbalances may reverse, in part, the impairment of cell mediated immunity in the elderly.[4]

Respiratory infections are a common cause of illness in old age[5] and may be life threatening. Immunisation against influenza virus is frequently administered in an attempt to reduce morbidity due to this infectious agent. Very little is known, however, about the immunological response to these vaccines in elderly people who have nutritional deficiencies. We therefore report how improved nutritional intake enhances antibody response to influenza virus vaccine in old age.

Subjects, methods, and results

During an epidemiological survey of the nutritional state of 100 elderly men, 30 aged 70-84 years were found who had abnormalities in at least two tests of clinical, biochemical (albumin, prealbumin, zinc concentrations), anthropometric (weight for height, skinfold thickness), and haematological (haemoglobin, ferritin values) fitness. Detailed nutritional data will be reported elsewhere. All the subjects lived independently in their own homes and none showed evidence of any acute or chronic serious systemic disease.

Each subject was inoculated with about 10^5 $TCID_{50}$ (median tissue culture infective dose) influenza A/Hong Kong/77 (H1N1). Serum samples for determination of antibody titres were obtained before immunisation and 28 days after inoculation. Serum haemagglutination inhibition antibodies were assayed by the use of chicken red blood cells and purified H1N1 influenza A antigen. A titre of $< 1/4$ before immunisation was considered seronegative and a fourfold or greater rise of antibody titre taken as evidence of seroconversion.

The 30 subjects were allocated at random to two groups. For four weeks beginning on the day of vaccination one group received nutritional advice and oral dietary and medicinal supplements appropriate for the type of malnutrition documented in each case. The second group of 15 served as non-supplemented controls. There was no significant difference between the groups in nutritional state, age distribution, socioeconomic state, housing, or other demographic features.

Dietary advice and supplements resulted in an improvement in nutritional state. At the end of four weeks changes in weight (58·7 (SD 6·1) *v* 63·9 (5·5) kg), skinfold thickness (11·0 (SD 2·7) *v* 14·8 (1·8) mm), and serum prealbumin concentration (230 (SD 40) *v* 460 (70) mg/l) were statistically significant. There was a trend towards improved values in other anthropometric, haematological, and biochemical tests as well. Moreover, there were fewer subjects showing abnormally low values.

Response to influenza virus vaccination in nutritionally supplemented elderly and non-supplemented controls

Group	No studied	No achieving seroconversion	Log reciprocal geometric mean antibody titre (SD)
Supplemented	15	14*	5·7 (1·2)†
Non-supplemented	15	9	2·5 (0·7)

*Compared with controls: $p < 0.05$ (χ^2 test corrected for continuity).
†Compared with controls: $p < 0.01$ (paired Student's *t* test).

Antibody response to influenza virus vaccination was significantly better in the supplemented group (table), as shown by a higher rate of seroconversion and a higher mean antibody titre.

Comment

The elderly make up a progressively growing segment of the population. A main health problem in old age is an increased incidence of infections, including respiratory illness.[5] In part, this may be the result of a progressive decline of immune function,[2] including depressed cell mediated immunity, decreased natural killer cell and phagocyte activity, and impaired epithelial barrier function.

Influenza virus infection is a common cause of serious respiratory illness in the elderly and may threaten survival. Hence vaccination is commonly given to this high risk group. Little is known, however, of the possible effect of frequently associated nutritional deficiencies on the immune response to the vaccine and the extent of protection achieved. In this study we observed a significantly increased rate of seroconversion and higher serum antibody titres in elderly men given nutritional supplementation for four weeks. Probably this improved immune response also confers better protection against influenza disease. It remains to be established, however, whether nutritional rehabilitation of elderly people *before* immunisation would have even greater beneficial effects in terms of both immune response as well as protection.

Nutritional deficiency is common in the elderly, and cell mediated immunity and other mechanisms of host resistance decline with aging. Since nutritional state is a critical determinant of immunocompetence, the correction of obvious or latent undernutrition in the elderly may be expected to improve immune responses, including that to vaccination against respiratory infections, and perhaps result in better protective immunity.

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