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LEVAMISOLE THERAPY IN ATAXIA-TELANGIECTASIA*

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Ataxia-telangiectasia (A-T) is a primary immunodeficiency disease characterized by progressive ataxia, oculocutaneous telangiectasia, recurrent sinopulmonary infections, various endocrine abnormalities, deficiency in serum IgA in cell-mediated immunity, and increased incidence of malignancies. It is transmitted in an autosomal recessive manner, but the etiology and pathogenesis remain unknown[1]. Various therapeutic measures have been unsuccessful in the treatment of A-T[2,3].

This report will present the in vivo effect of levamisole (LMS), a drug known as an immune potentiator, on the cellular immune response of patients with A-T.

Material and Methods

Nine patients previously diagnosed as having ataxia-telangiectasia were given LMS. The therapy, which lasted two months, consisted of intermittent administration of LMS (doses ranging from 1.25 to 2 mg/kg, or a total of 40 mg/day) for 3 days at the beginning of each 2-week period. Every patient was examined clinically and radiologically for the presence of sinusitis and lung infection. Moreover, serum immunoglobulins and cell-mediated immunity (total lymphocyte count, skin tests, E rosettes, blastogenic transformation) were checked before and after LMS therapy according to previously published methods[3]. Their results were analyzed statistically for paired means by the chi-square and Student t tests.

Findings

Six of the nine patients had sinusitis, and three showed clinical and radiological responses to the combination of antibiotics and LMS. However, pulmonary disease (chronic fibrotic changes in four patients and bronchiectasis in one) and neurological findings persisted after LMS administration. No side effects of the drug were observed except in one patient (S.Y.) who developed neutropenia (1596/μl); in that instance the neutrophil count reached normal values after cessation of LMS.

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The total lymphocyte count (TLC) and total E rosettes of the A-T patients were significantly low ($p < 0.05$) when compared to those of normal age-matched controls (Table I). With LMS treatment, the mean total lymphocyte count and mean absolute number of E rosettes showed significant increases compared to the pre-treatment values, but the mean percentage of E rosettes showed no change.

The candida skin test remained negative in all patients. The negative skin tests were converted to positive in two patients (AO, AT) for PHA, in one patient (IB) for PPD, and in three patients (AO, ND, AT) for SKSD, and the diameter of the indurations for PHA skin testing was found to be larger in five patients following LMS treatment. We observed no improvement in the in vitro (blastogenic) response of lymphocytes to PHA or candida and SKSD antigens with the LMS therapy. In fact, the percent responding before and after therapy was 52.1% (12/23) and 44.4% (13/27), respectively (Table II).

Two patients in our series (SY, SÖ) had low serum IgA values. The mean serum IgG and serum IgA levels showed no significant differences before (855 ± 115 mg/dl for IgG, 101 ± 58 mg/dl for IgA) or after (859 ± 151 mg/dl for IgG, 103 ±71 mg/dl for IgA) LMS treatment. However, we observed elevated serum IgM levels (mean 198 ± 58 mg/dl, range 112-252 mg/dl) which became significantly decreased ($p < 0.01$) (mean 151 ± 48 mg/dl, range 85-217 mg/dl) following LMS administration.

TABLE I

TOTAL LYMPHOCYTE COUNT (TLC) AND E ROSETTES

Patients	Years of age / sex	TLC/μl		E rosettes %		E rosettes (absolute / μl)	
		B	A	B	A	B	A
A.O.	8/M	2080	2318	56	47	1164	1089
H.A.	12/M	1444	1504	51	65	736	977
E.Y.	8/M	1332	2100	66	53	879	1113
S.Y.	12/F	1120	2184	60	59	672	1289
S.Ö.	5/F	2100	1400	36	41	756	574
I.B.	7/F	2800	4176	54	56	1512	2339
N.D.	10/F	1820	3432	50	40	910	1373
C.D.	8/M	1300	2652	53	57	689	1512
A.T.	12/M	2016	4896	68	73	1371	3574
Patients (mean ± SD)		1799 ± 532	2740 ± 1194	54.8 ± 9.5	54.5 ± 10.7	965 ± 310	1537 ± 901
Controls (mean ± SD) (n = 15)		1954 ± 527		60.2 ± 7.8		1162 ± 289	

B: Before therapy A: After therapy

TABLE II

SKIN TESTS AND BLASTOGENIC TRANSFORMATION

Patient	Years of age/sex	Skin Tests* PHA B	PHA A	Candida B	Candida A	PPD B	PPD A	SKSD B	SKSD A	Blastogenic transformation SI** PHA		Candida		SKSD	
A.O.	8/M	–	+	–	–	–	–	–	+	178	165	5.2	0.7	0.8	0.4
H.A.	12/M	+	++	–	–	+	+	–	–	32	24	3.0	2.3	ND	0.3
E.Y.	8/M	+	++	–	–	–	–	–	–	105	15	6.5	3.0	1.6	1.0
S.Y.	12/F	++	+	–	–	–	–	+++	++	152	62	3.8	1.2	5.5	2.8
S.Ö.	5/F	+	+++	–	–	–	–	–	–	ND	74	ND	22	ND	2.8
I.B.	7/F	++	+++	–	–	–	+	+++	+++	131	8.0	1.1	17	1.0	1.1
N.D.	10/F	++	+++	+	–	–	–	–	+	66	26	1.3	1.3	1.0	0.7
C.D.	8/M	++	++	–	–	–	–	–	–	33	16	1.1	2.3	1.0	0.7
A.T.	12/M	–	+	–	–	–	–	–	+	18	1.0	0.6	0.6	0.3	0.7
Total number responding		7:9	7:9	0:9	0:9	1:9	2:9	2:9	5:9	7:8	5:9	4:8	5:9	1:7	3:9

B: Before therapy A: After therapy ND: not determined

* –: Negative, + = positive (indurations 5-10 mm = +, 10-15 mm = ++, > 15 mm = +++)

** SI: Stimulation index (CPM stimulated/CPM unstimulated; an index > 20 for PHA and > 2 for antigens is considered a response.)

Discussion

LMS has been reported to increase the cellular immune responses in anergic patients[5]. It has been shown that this drug restores cutaneous delayed hypersensitivity reactions [5], enhances E rosette formation[6] and stimulates in vitro production of soluble mediators by mitogen-stimulated lymphocytes[7]. Several investigators have studied the effect of LMS on the proliferative response of human lymphocytes in vitro. In all but one of these studies, LMS had no effect on in vitro lymphocyte proliferation[5,8,9]. The increase in the lymphokine production was observed in the presence of levamisole with suboptimal doses of antigen or mitogen[7,9]. Despite wide use of LMS in various kinds of malignancies, viral diseases, immunodeficiency states, rheumatoid arthritis, systemic lupus erythematous, and other clinical conditions, the mechanism by which the interaction of LMS with the immune response induces clinical improvements remains puzzling. It has been reported that LMS enhances the catabolism of cyclic AMP and inhibits the catabolism of cyclic GMP which is implicated in the process of lymphocyte activation[10]. The immunostimulation induced by this drug is reported to be associated more with the activities of its sulphur moiety than with the cholinergic properties of the imidazole moiety. LMS activities are modulated by genetic and environmental factors and by the degree of antigenic stimulus, and immunostimulation by LMS depends upon individual responsiveness[11].

Verhaegen et al[6] reported the alleviation of recurrent bronchial infections, but no change in the IgA level, in a 4-year-old boy with A-T following five months of LMS therapy. The neurological symptoms were claimed to be less pronounced in this patient and E rosette percentage was found to be increased from 50.5% to 61%.

In our study we investigated the in vivo effects of LMS therapy on 9 patients with A-T. Following a 2-month course of therapy, we found the total number of lymphocytes and total number of E rosettes to be increased. However, there were no changes in the percentage of E rosettes or in the blastogenic response to antigens (candida, SKSD) or PHA. LMS therapy did not cause any striking restoration of cutaneous hypersensitivity reactions, but serum IgM levels were decreased significantly. Clinically, LMS had no effect on the neurological findings although episodes of fever were decreased and sinusitis in 3 patients was found to be cleared.

Summary

The in vivo effects of LMS were studied in 9 patients with A-T for a two month period. Among the various immunological parameters investigated following treatment with LMS, only the total lymphocyte count and the absolute number of E rosettes were found to be increased and serum IgM levels were reduced.

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