CLINICAL RESEARCH

Atopic manifestations in the acquired immune deficiency syndrome: response to recombinant interferon gamma

JACQUELINE M PARKIN, LESLEY-JANE EALES, ANDREW R GALAZKA, ANTHONY J PINCHING

Abstract

Six patients with the acquired immune deficiency syndrome (AIDS) had exacerbations or recurrences of previously quiescent atopic disease when they developed immunodeficiency. Four developed a different atopic illness from that suffered previously. Atopic symptoms developed within three months after the patients developed AIDS or during prodromal illness. Two of the patients were treated with recombinant interferon gamma: both showed a striking improvement in symptoms and cellular immunity.

These results indicate that cellular immunity, through interferon gamma, may have a role in regulating atopic disease.

Introduction

The mechanisms underlying induction and control of the allergic response in man are incompletely understood. The observation of a recrudescence of previously quiescent atopic disease in adults with the acquired immune deficiency syndrome (AIDS) prompted a study of its pathogenesis; in two of the patients we assessed the effect of giving interferon gamma.

Patients, methods, and results

A history of allergic disease was sought in 16 consecutive patients in whom AIDS was diagnosed and in one patient seen previously. Prick testing for immediate hypersensitivity was performed by standard methods with 16 common allergens and for delayed hypersensitivity with three standard antigens. Total serum IgE concentrations were measured with a paper

radioimmunosorbent test (Prist, Pharmacia). Lymphocyte subsets and lymphokine production were also estimated.¹

Seven patients had a history of atopic disease (asthma, eczema, or hay fever) in childhood or adolescence (table); in one this had persisted into adult life. In the five patients who had "grown out of" their allergies, atopic symptoms recurred when they became immunodeficient. In a further patient atopic symptoms increased at this time. None of the 10 patients without previous atopic disease developed atopic symptoms within a year after the diagnosis of AIDS. There were no appreciable differences in age, time from diagnosis, or manifestations of AIDS between the two groups.

Two of the seven patients with atopy, but none of the others, had a family history of atopy. Four of the six patients with a recurrence or exacerbation of symptoms developed a different atopic disorder from that suffered previously. Atopic symptoms occurred within three months after the patient developed AIDS or during prodromal illness, when they were temporally associated with signs of early immunodeficiency—that is, chronic mucocutaneous herpes simplex or candidiasis, or both.

The patients with atopy had evidence of increased type I hypersensitivity with more positive results on prick testing (mean 9, range 6–12) than the others (mean 2, range 0–4). There were no significant differences between the two groups in IgE concentrations (mean 158.2 kU/l in atopic patients compared with 200.6 kU/l in the others) or in T₄ (CD4) cell counts or delayed type hypersensitivity responses.

Two patients showed striking improvement in their atopic symptoms during a trial of recombinant interferon gamma (Immuneron; Biogen, Geneva); they received twice weekly intravenous infusions of 5.1 × 10⁷ units/m² (case 2) and 1.7 × 10⁷ units/m² (case 5) for eight weeks. One patient (case 2) had developed angio-oedema after ingesting milk: mucosal swelling occurred within five to 10 minutes, even after diluted milk; after eight weeks' treatment she tolerated undiluted milk without symptoms. The other patient had asthma needing daily inhaled salbutamol. After four weeks' treatment this had resolved, and he remained asymptomatic. His asthma gradually returned four weeks after he stopped taking interferon gamma but resolved on reintroduction of the drug. Both patients had concomitant immunological improvement during treatment, shown by (1) conversion of one third of previously negative tests of delayed type hypersensitivity; (2) increase in T₄ lymphocytes (0.26 to 0.43 × 10⁹/l and 0.48 to 0.77 × 10⁹/l); (3) production of interferon gamma (and interleukin 2 in case 5) by unstimulated and mitogen stimulated lymphocytes (previously absent); and (4) a decreased number of Kaposi's sarcoma lesions (from six to one in case 5).

Discussion

Patients with AIDS who have a history of atopic disease develop a recurrence of atopic symptoms when they become immuno-

Department of Immunology, St Mary's Hospital Medical School, London W2
JACQUELINE M PARKIN, MB, Wellcome research fellow
LESLEY-JANE EALES, PHD, research fellow
ANTHONY J PINCHING, DPHIL, FRCP, senior lecturer and honorary consultant

Biogen Medical Research, Geneva, Switzerland
ANDREW R GALAZKA, MB, director of clinical research

Correspondence to: Dr Pinching.

Atopic history in patients with the acquired immune deficiency syndrome

Case No	Age and sex	Diagnosis of AIDS	Atopic history	Age when symptoms present (years)	Atopic symptoms related to AIDS	Temporal relation to AIDS	Family history
1	27 M	Kaposi's sarcoma, <i>Pneumocystis carinii</i> pneumonia	Asthma	8-12	Hay fever, reaction to cat fur*	Occurred with persistent generalised lymphadenopathy	None
2	49 F	<i>P. carinii</i> pneumonia	Hay fever	16-20	Asthma, reaction to milk†	Asthma developed three years before AIDS; incubation period of human immunodeficiency virus was at least five years, suggesting an association. Reaction to milk developed one month after AIDS	Son and grandmother
3	36 M	<i>P. carinii</i> pneumonia, oesophageal candidiasis	Asthma	14	Eczema, hay fever	Occurred with persistent generalised lymphadenopathy	Mother
4	21 M	Mycobacterial pneumonia	Eczema	2-8	Hay fever	Occurred with persistent generalised lymphadenopathy	None
5	36 M	Kaposi's sarcoma	Asthma, hay fever	5-18, 5-10	Asthma	Developed three months after AIDS	None
6	47 M	Kaposi's sarcoma, <i>P. carinii</i> pneumonia	Asthma, eczema	From childhood	Asthma, eczema	Considerable increase in asthma; eczema developed with Kaposi's sarcoma	Not known
7	51 M	<i>P. carinii</i> pneumonia	Hay fever	From childhood	No change		None

*Rhinitis, sneezing, and conjunctivitis on exposure.

†Swelling of tongue and lips 5-10 minutes after every exposure to milk.

deficient. They characteristically show defective cell mediated immunity with reduced numbers and function of T₄ lymphocytes, including decreased production of interleukin 2 and interferon gamma.² Total IgE concentrations were not higher in the atopic patients with AIDS, but the results of prick testing suggest that specific IgE may be increased. The IgE response is regulated by factors derived from T cells and induced by substances, possibly interferons, that are derived from macrophages.³

This study provided striking evidence for the *in vivo* activity of recombinant interferon gamma. Improvement in the atopic symptoms may have been caused by a direct effect of interferon gamma on mediation of the allergic response—for example, by influencing the cellular control of IgE production or by a peripheral effect on mast cell binding of or responsiveness to IgE.

Although an increased incidence of atopic eczema has been noted in children with AIDS,⁴ this is the first documentation of exacerbation of atopy in adults. We have provided evidence that cellular

immunity, apparently through interferon gamma, has a role in regulating atopy; this has implications for the pathogenetic mechanisms underlying atopic disease in general.

We thank the patients, without whom this work would not have been possible. The work was supported partly by the Medical Research Council and partly by Biogen Medical Research.

References

- 1 Eales L-J, Moshtael O, Pinching AJ. Microbicidal activity of monocyte derived macrophages in AIDS and related disorders. *Clin Exp Immunol* 1986;67:227-35.
- 2 Pinching AJ, Weiss RA. AIDS and the spectrum of HTLV-III/LAV infection. *Int Rev Exp Pathol* 1986;28:1-44.
- 3 Ishizaka K. Regulation of IgE synthesis. *Annual Reviews of Immunology* 1984;2:159-82.
- 4 Scott GB, Buck BE, Leterman JG, Bloom FL, Parks WP. Acquired immunodeficiency syndrome in infants. *N Engl J Med* 1984;310:76-81.

(Accepted 28 October 1986)

Exaggerated postural vasoconstrictor reflex in Raynaud's phenomenon

NIELS OLSEN, OSGAR ULF PETRING, NIELS ROSSING

Abstract

The central and local regulation of capillary blood flow in the finger was studied by the local xenon¹³³ washout technique in women with primary Raynaud's phenomenon, men with vibration induced white finger, and their respective sex matched controls. The vasoconstrictor response to venous stasis of 40 mm Hg elicited by local reflex was normal in both types of

Raynaud's phenomenon. Change in posture from lying to sitting induced vasoconstriction in all groups, which was abolished by proximal nervous blockade. The vasoconstrictor response to sitting was augmented in both groups of subjects with Raynaud's phenomenon compared with their sex matched controls.

These results show the existence of central and local postural vasoconstrictor reflexes in normal fingers. In both types of Raynaud's phenomenon there was hyperactivity of the central sympathetic nervous system to orthostatic stress and normal function of digital arterioles and postganglionic sympathetic nerve fibres.

Introduction

Raynaud's phenomenon is episodes of well demarcated pallor of one or more fingers brought on by cold. Raynaud's original proposal of hyperactivity of the central sympathetic nervous system¹ and the later assertion by Lewis of a "local digital vascular fault"² remain the

Department of Clinical Physiology and Nuclear Medicine and Clinic of Occupational Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

NIELS OLSEN, MD
OSCAR ULF PETRING, MD
NIELS ROSSING, MD

Correspondence and requests for reprints to: Dr Niels Olsen, Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen Ø, Denmark.