

A REVIEW OF AETIOLOGICAL FACTORS IN ERYTHEMA MULTIFORME

THELMA H. HUTCHISON, M.B.

Clinical Assistant, Dermatology Department, Belfast City Hospital

AGNESE M. T. KELLY, M.D., D.C.H.

Consultant, Dermatology Department, Belfast City Hospital

HELEN MAWHINNEY, M.D., M.R.C.P. (U.K.)

Senior Lecturer/Consultant in Clinical Immunology
Departments of Medicine, Microbiology and Immunobiology
The Queen's University of Belfast

THE clinical syndrome of erythema multiforme extends from a mild rash with typical target lesions of the hands and feet to a severe illness with widespread involvement of the skin and mucous membranes as in the Stevens-Johnson syndrome (Stevens and Johnson, 1922). It has been reported to occur in association with a number of different stimuli after an interval of one to three weeks (Champion, 1972; Shelley, 1967). The list of associated factors is large and some are included on the basis of single case reports. There has, however, been no comprehensive survey demonstrating the relative importance of the various aetiological factors involved in erythema multiforme of all degrees of severity in an unselected group of patients. We therefore undertook a retrospective study of all patients newly diagnosed as having erythema multiforme over a three-year period throughout Northern Ireland.

PATIENTS AND METHODS

The hospital records of all dermatology departments throughout Northern Ireland were examined. During the years 1972 to 1974 a total of 184 patients were classified as having erythema multiforme, including those with the Stevens-Johnson syndrome. A questionnaire was sent to 162 patients in whom a confident clinical diagnosis of erythema multiforme had been made. The information obtained from the questionnaires was correlated with the hospital records available for each patient.

RESULTS

Eighty-five (52.5 per cent) out of the 162 questionnaires were returned completed. In analysing the information obtained it became apparent that the conclusions which could be drawn from a single episode of erythema multiforme were limited. Accordingly the patients were subdivided into two groups, those having had more than one attack and those having had a single attack of erythema multiforme.

Patients having had more than one attack of erythema multiforme

The incidence of reported precipitating factors in this group of patients is shown in Table 1. A total of 27 (62.8 per cent) out of 43 patients had herpes

simplex infection in association with erythema multiforme. Other infections were less commonly associated with erythema multiforme in these patients, a single patient having had a sore throat preceding an attack of erythema multiforme on two occasions. Drugs were associated with the rash in two patients, the drugs concerned being trimethoprim-sulphamethoxazole (Septrin) and pentazocine hydrochloride (Fortral). Various other factors such as pregnancy, sunlight and contact dermatitis produced an erythema multiforme type of rash in five patients on two or more occasions. One patient produced the rash in response to a wasp sting on one occasion and later in association with impacted wisdom teeth. In seven (16.3 per cent) out of 43 patients who had more than one attack of erythema multiforme, no obvious precipitating factor was reported.

TABLE 1: REPORTED PRECIPITATING FACTORS IN 85 PATIENTS WITH ERYTHEMA MULTIFORME

<i>Precipitating factors</i>		<i>Patients with more than one attack (per cent)</i>	<i>Patients with one attack only (per cent)</i>
Herpes simplex infection	-	27 (62.8)	4 (9.5)
Other infection	-	1 (2.3)	4 (9.5)
Drugs	-	2 (4.7)	1 (2.4)
Drugs and infection	-	0	5 (11.9)
Miscellaneous factors	-	6 (13.9)	6 (14.3)
No obvious factor	-	7 (16.3)	22 (52.4)
Number of patients	-	43	42
Percentage of total	-	50.6	49.4

Patients having had a single attack of erythema multiforme

The incidence of the various types of precipitating factor in this group of patients is shown in Table 1. Only four (9.5 per cent) patients out of a total of 42 patients who had a single attack of erythema multiforme had associated herpes simplex lesions. In four patients single attacks followed infections other than herpes simplex. These infections were orf, streptococcal throat, measles and smallpox vaccine. In addition, five patients had a single attack of erythema multiforme in association with an infection for which a drug was prescribed as shown in Table 2. However, in these patients it is difficult to know whether the drug, or the infection for which it was prescribed, was the relevant aetiological factor. A drug was the single factor associated with an attack of erythema multiforme in only one patient, the drug being phenylbutazone. Miscellaneous factors, pregnancy in two patients and insect bites in three patients, were associated with a single episode of erythema multiforme, while in one patient the final diagnosis was dermatitis herpetiformis though the initial presentation was that of erythema multiforme. No obvious precipitating factor was found in a total of 22 (52.4 per cent) of this group of patients.

TABLE 2: INFECTION AND CONCURRENT DRUG THERAPY ASSOCIATED WITH
A SINGLE ATTACK OF ERYTHEMA MULTIFORME

<i>Infection</i>				<i>Drug</i>
Sinusitis	-	-	-	Clindamycin
Diarrhoea	-	-	-	Trimethoprim-sulphmethoxazole
Throat infection	-	-	-	Penicillin
Tooth socket infection	-	-	-	Novobiocin sodium and streptomycin
Infected Bartholin's cyst	-	-	-	Ampicillin

DISCUSSION

Although it has been accepted for many years that there is an association between herpes simplex infection and erythema multiforme (Urbach, 1933; Forman and Whitwell, 1934; Anderson, 1945), there have been few attempts to determine the relative incidence of this and other possible aetiological factors in a series of unselected patients with erythema multiforme. It has been stated that the association of herpes simplex lesions with erythema multiforme could be observed in more than 15 per cent of patients who have recurring erythema multiforme (Shelley, 1967). In our study, however, herpes simplex infection was associated with the rash in 62.8 per cent of patients with recurrent erythema multiforme, but by contrast only 9.5 per cent of patients with a single attack of erythema multiforme had associated herpes simplex infection. The recurrent nature of herpes simplex infection is the most probable explanation for the striking difference between the incidence of associated herpes simplex in these two groups. In addition, since this was a retrospective study in which patients have completed a questionnaire at least nine months after the attack with which they presented, it is probable that any patient with latent herpes simplex will have had further overt attacks. It is also perhaps relevant that this study has been carried out in a population in which herpes simplex virus-specific IgG antibody is found in 84 per cent of healthy blood donors when the sera were tested at a serum dilution of 1:5 (Haire, Frazer and Millar, 1973).

Recently, evidence has been produced of an association between herpes simplex virus type 2 (herpes genitalis) and erythema multiforme (McDonald and Feiwel, 1972; Britz and Sibulkin, 1975). In our study no patients were recorded as having herpes genitalis at the time of presentation though vaginal examination was not routinely carried out on all female patients.

Several groups of workers have suggested an association between *Mycoplasma pneumoniae* infection and both the Stevens-Johnson syndrome and erythema multiforme minor (Ludlam, Bridges and Benn, 1964; Gordon and Lyell, 1970). In our series we found little evidence to associate erythema multiforme with infections which might have been of mycoplasmal origin. Nevertheless, it is relevant that the incidence of *Mycoplasma pneumoniae* infection in Northern Ireland is relatively high, antibody being present in low titre in approximately 70 per cent of the population (Connolly, 1976).

Many different drugs have been cited as possible aetiological factors in the production of erythema multiforme throughout its clinical range from a relatively minor complaint to the Stevens-Johnson syndrome (Bianchine *et al*, 1968; Shelley, 1967). In our study a drug was the single factor associated with erythema multiforme in only 7.1 per cent of patients while drugs were possibly involved in a further 11.9 per cent of patients.

The relative importance of drug-induced erythema multiforme may vary with variations in drug-prescribing habits. In the past (B.M.J. Leading Article, 1964; Carroll, Bryan and Robinson, 1966) long-acting sulphonamides have been a major association with erythema multiforme including the Stevens-Johnson syndrome. These drugs are now less commonly prescribed but it is interesting to note that in our series a drug combination (trimethoprim-sulphamethoxazole) containing a sulphonamide produced erythema multiforme on five occasions in one patient and may have been responsible for a single attack in another patient.

In view of the high proportion of herpes-associated cases in recurrent erythema multiforme in this series, further investigation might usefully concentrate on this group of patients and on the possible role of immunological mechanisms in producing the skin lesions.

SUMMARY

A retrospective study of 85 patients with erythema multiforme was undertaken by means of a questionnaire.

In 43 patients with more than one attack of erythema multiforme the attacks were associated with herpes simplex infection, throat infection, drug administration, and other miscellaneous factors in 27, 1, 2 and 6 patients respectively. There was no obvious associated factor in 7 patients.

ACKNOWLEDGMENTS

We thank the consultant dermatologists of Northern Ireland for permission to study their patients, and Dr. Margaret Haire and Dr. Grace E. Allen for their advice and encouragement.

This work was carried out when one of us (T.H.H.) was in receipt of a grant from the Eastern Health and Social Services Board.

REFERENCES

- ANDERSON, N. P. (1945). Erythema multiforme: Its relationship to herpes simplex. *Archives of Dermatology and Syphilology*, 51, 10.
- BIANCHINE, J. R., MACARAIG, P. V. J., LASANGA, L., AZARNOFF, D. L., BRUNK, S. F., HVIDBERG, E. F. and OWEN, J. A. (1968). Drugs as etiological factors in the Stevens-Johnson syndrome. *American Journal of Medicine*, 44, 390.
- BRITISH MEDICAL JOURNAL (1964) Leading article. Stevens-Johnson syndrome from long-acting sulphonamides. 2, 1410.
- BRITZ, M. and SIBULKIN, D. (1975). Recurrent erythema multiforme and herpes genitalis (type 2). *The Journal of The American Medical Association*, 233, 812.

- CARROLL, O. M., BRYAN, P. A. and ROBINSON, R. J. (1966). Stevens-Johnson syndrome associated with long-acting sulphonamides. *The Journal of The American Medical Association*, 195, 691.
- CONNOLLY, J. H. (1976). Personal Communication.
- CHAMPION, R. H. (1972). In: Textbook of Dermatology (ed. by A. J. Rook, F. J. Ebling and D. S. Wilkinson), 2nd edn. p 891. *Blackwell Scientific Publications, Oxford*.
- FORMAN, L. and WHITWELL, G. P. B. (1934). The association of herpes catarrhalis with erythema multiforme (Hebra). *British Journal of Dermatology*, 46, 309.
- GORDON, A. M. and LYELL, A. (1970). Mycoplasmas and their association with skin disease. *British Journal of Dermatology*, 82, 414.
- HAIRE, M., FRASER, K. B. and MILLAR, J. H. D. (1973). Virus-specific immunoglobulins in multiple sclerosis. *Clinical and Experimental Immunology*, 14, 409.
- LUDLAM, G. B., BRIDGES, J. B. and BENN, E. C. (1964). Association of Stevens-Johnson syndrome with antibody for mycoplasma pneumoniae. *Lancet*, i, 958.
- MACDONALD, A. and FEIWEL, M. (1972). Isolation of herpes virus from erythema multiforme. *British Medical Journal*, 2, 570.
- SHELLEY, W. B. (1967). Herpes simplex virus as a cause of erythema multiforme. *The Journal of the American Medical Association*, 201, 153.
- STEVENS, A. M. and JOHNSTON, F. C. (1922). A new eruptive fever associated with stomatitis and ophthalmia. *American Journal of Diseases of Children*, 24, 526.
- URBACH, E. (1933.) Herpes labialis, erythema exsudativum multiforme. *Zentralblatt fur und Geschlechtskrankheiten*, 46, 413.