The Ulster Medical Journal, Volume 55, No. 2, pp. 172 – 174, October 1986.

Case report

Methyldopa-induced connective tissue disorder

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Accepted 21 July 1986.

Several drugs are known to cause a lupus-type syndrome.[1] Methyldopa causes positive anti-nuclear antibody reactions, but only two previously reported cases of a methyldopa-induced lupus-type syndrome have been described.[2,3] We report a case of this syndrome which failed to resolve fully on withdrawal of the drug, and which has features of a mixed connective tissue disorder (MCTD).

CASE HISTORY

A 78-year-old woman presented in March 1985 with myalgia, arthralgia, loss of energy and postural dizziness. Drug therapy prior to admission was methyldopa 500 mg three times daily and cyclopenthiazide 500 µg daily, which she had taken for four years for 'hypertension', and naftidrofuryl oxalate 100 mg three times daily.

On examination she had severe postural hypotension (supine blood pressure 140/80 mmHg, erect 80/40 mmHg), generalised muscle tenderness, marked leg oedema and ascites. The ESR was 106 mm/hour, Hb 11.7 g/dl, WCC $13.1 \times 10^9/l$ (eosinophils $2.22 \times 10^9/l$), urea and electrolytes normal, total protein 49 g/l, alkaline phosphatase 62 u/l, aspartate transaminase 28 u/l, alanine transaminase 13 u/l and gammaglutamyltransferase 5 u/l. Plasma protein electrophoresis showed generalised hypergammaglobulinaemia. Serum creatinine was 123 µmol/l, creatinine clearance 30 ml/min, urinary protein output 0.14 g/24 hours. Serum C_3 and C_4 complement levels were normal. Anti-nuclear antibodies (ANA) were present, titre 1:320 (IgG class, diffuse pattern) but antibodies to double-stranded DNA and to ribonucleoprotein were negative. The chest X-ray showed a moderate right-sided pleural effusion.

All her drugs were stopped and, at review one month later, her postural hypotension had resolved. The ESR was 30 mm/hour, the WCC $10.9 \times 10^9/l$ (eosinophils $0.26 \times 10^9/l$) and the total serum protein had risen to 63 g/l. The pleural effusion had resolved radiologically and the ascites had cleared. At this review, she had severe Raynaud's phenomenon and complained of 'taut, tight skin' on hands and feet. There was a violaceous rash on the extensor surfaces of elbows and knees and around the eyes suggestive of dermatomyositis. There were discrete telangiectatic areas over the hands, and the skin appeared

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thickened, tight and shiny over hands, forearms and knees. A skin biopsy showed oedema only and was negative for immunofluorescent antibody staining. Despite this, the clinical appearances were typical of sclerodermatous change. Barium swallow demonstrated oesophageal hypomotility and pooling of barium in the erect position suggesting systemic involvement. X-rays of both hands were negative for soft tissue calcification.

COMMENT

A drug-induced lupus-type syndrome was first associated with hydrallazine in 1953.[4] Since then, over 30 drugs have been implicated,[5] the commonest being hydrallazine and procainamide.[1] As far as we are aware, this is only the third reported case of methyldopa-induced lupus-type syndrome.

In contrast with systemic lupus erythematosus, drug-induced lupus is commoner in older patients and tends to run a benign clinical course. Renal and neurological involvement is rare and the clinical syndrome usually remits following withdrawal of the offending drug. Our patient had certain unusual features of the drug-induced lupus syndrome. Although her pleural effusion and ascites resolved spontaneously following drug withdrawal, she rapidly developed severe Raynaud's phenomenon and cutaneous features of scleroderma and dermatomyositis. These have persisted for nine months following withdrawal and she remains positive for ANA. This contrasts with most reported cases of drug-induced lupus in which symptoms and signs have remitted promptly following drug withdrawal. However, in one of the two previously reported cases the positive ANA persisted for three months following drug withdrawal, though in this case the clinical syndrome itself resolved rapidly within two weeks of drug withdrawal.[2] The fact that the positive ANA can persist indicates that the drug-induced auto-immune condition can also persist. It is therefore possible that our patient's condition persisted and evolved into a sclerodermatous condition following withdrawal of the methyldopa. The combination of arthralgia, myalgia, Raynaud's phenomenon, oesophageal hypomotility and cutaneous features of scleroderma and dermatomyositis raises the possibility of mixed connective tissue disease despite the fact that serum was repeatedly negative for ribonucleoprotein antibodies.

Seroconversion to positive ANA has occurred in the known cases of methyldopa-induced lupus syndrome after variable periods of drug exposure. Breckenridge et al showed that ANA positively rises with duration of treatment.[6] In the two previously reported cases, the duration of treatment before seroconversion was two years and one year respectively[2, 3] and in our patient it was four years. The development of ANA and the lupus-type syndrome in patients taking methyldopa is therefore probably dose-related. Inhibition of suppressor T cell functions by methyldopa has been demonstrated and may be one of the factors responsible.[7]

This patient demonstrates some unusual features of methyldopa-induced lupus syndrome and is only the third reported case. The clinical presentation and progress raises the possibility of an associated mixed connective tissue disease. We cannot recommend the use of methyldopa as an anti-hypertensive agent in the elderly because of its association, in our experience, with central nervous system depression, postural hypotension, haemolytic anaemia, cholestatic jaundice and now a lupus-type syndrome.

We thank Dr M Haire for supplying the autoantibody measurements, and Dr G Allen for dermatological advice.

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