CASE REPORTS

Focal fits during chlorambucil therapy

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Summary

An elderly man receiving chlorambucil for chronic lymphatic leukaemia developed focal fits. The onset and frequency were dose related. There was no evidence of metabolic disturbance or of meningeal leukaemia. Although reported in children and well recognized in animals, chlorambucil-induced fits in an adult have not been previously recorded.

Introduction

Chronic lymphatic leukaemia is a disease of the elderly with a long natural history. Treatment is palliative, with chlorambucil the drug of choice (Livingston and Carter, 1970). The recognized side effects of chlorambucil include nausea, myelosuppression, skin eruptions and pulmonary fibrosis (Stenfert Kroese, 1975), but their incidence is low. Although high doses of chlorambucil are epileptogenic in animals (Pradhan and Marsan, 1963) only recently have fits been attributed to chlorambucil therapy, and this in childhood (Williams, Makker and Grupe, 1978). There have been no previous reports of fits in an adult receiving chlorambucil.

Case report

In 1965, a 63-year-old man presented with anaemia and hepatosplenomegaly. Chronic lymphatic leukaemia was diagnosed. He developed intermittent claudication in 1973, and in 1974 chlorambucil was prescribed in a dose of 2 mg/day. There was a rapid fall in his white cell count and therapy was discontinued after 2 months. A further 2-month course of chlorambucil (2 mg/day) was given in 1975. The patient experienced no side effects of therapy.

He required no further treatment for 2 years, but then developed angina, anaemia and a white cell count of $490 \times 10^9/l$ (100% lymphocytes) for which he was given chlorambucil (5 mg/day) with allopurinol (300 mg/day). Three weeks later he had 2 focal fits, each starting in the right arm, and was admitted to hospital the same day. Five hours after

admission a third focal fit was witnessed. There was no residual neurological deficit. The plasma urea, electrolytes, glucose, calcium and phosphate and an EEG were normal. All drugs were withdrawn, and over the next 4 days no further fits occurred.

Chlorambucil was then restarted in a dose of 10 mg/day. An EEG that day showed an intermittent widespread minor abnormality with slight left-sided preponderance, but no focal or epileptiform features. Seventeen hours after restarting chlorambucil, a further fit occurred, and phenytoin was begun.

The following day 5 fits were observed, and the patient exhibited epilepsia partialis continua of the right hand with a flaccid paresis of the right arm and leg. An EEG showed continuous widespread theta activity, with sharp waves (amplitude up to $65 \mu V$) but without focal features. No further chlorambucil was given, but allopurinol and phenytoin were continued and carbamazepine was added.

Thereafter no more fits occurred, and function returned to the right arm and leg over the next week. A third EEG, 13 days after withdrawing chlorambucil, showed appearances very similar to the initial one. Isotope and computerised axial tomography (CAT) brain scans were both normal. A lumbar puncture yielded clear CSF with no evidence of meningeal leukaemia. The whole blood viscosity was not increased, and the white cell count during this time ranged from 290 to $330 \times 10^9/l$.

The anti-convulsant therapy was gradually withdrawn and the patient discharged from hospital. No further fits had occurred before the patient died from bronchopneumonia at home, 10 months after admission.

Discussion

High doses of chlorambucil reproducibly cause centrencephalic epilepsy in rabbits and cats (Pradhan and Marsan, 1963), monkeys (Mirsky, Bloch-Rojas and McNary, 1966) and rats (Pinel and Chorover, 1972). Similar EEG changes have been recorded in a

17-year-old patient receiving chlorambucil for choriocarcinoma (Pradhan and Marsan, 1963). Fits have also been reported following overdosage in a child (Wolfson and Olney, 1957). Recently, fits have been reported in 7 out of 91 children receiving relatively high therapeutic doses of chlorambucil for glomerulonephritis. In 6 of the children the fits were focal, at least initially (Williams *et al.*, 1978). Only one of the children had suffered previous seizures. The EEG showed focal (4 children) or diffuse (2 children) abnormalities. When the chlorambucil was withdrawn, seizure activity did not recur. Follow-up EEGs were obtained in 5 of the children, and were normal.

In the case reported here, the onset of fits was twice associated with chlorambucil therapy. They were more frequent and occurred sooner at the higher dose. The relationship of fit frequency to dose level may explain why no fits occurred during the previous 2-month courses of 2 mg/day. Although the patient had both angina and intermittent claudication and may well have had cerebro-vascular disease, there was no previous history of epilepsy. After withdrawing chlorambucil it was possible to stop all anti-epileptic therapy without the fits recurring.

It is likely, therefore, that chlorambucil precipitated this patient's fits, since they recurred when the drug was reintroduced. While clearly uncommon, chlorambucil-induced epilepsy should be considered when convulsions occur in a patient receiving the

drug. Although the EEG in experimental chlorambucil-induced epilepsy often resembles petit mal, Palestini *et al.* (1973) obtained evidence of asynchrony in cats. This may explain the frequent occurrence of focal seizures in patients with chlorambucil-induced epilepsy. However, the focal nature of the fits in the patient reported here may be related to cerebrovascular disease.

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