Iatrogenic encephalopathy

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DIRECT involvement of the central nervous system as an allergic response to drugs is uncommon. This report is of a patient who developed a rash and an encephalopathy, probably as a reaction to drugs. A similar occurrence has not been recorded in response to any of the three drugs (triclofos, dichloralphenazone and chlorpromazine) which the patient was taking, nor has the clinical picture seen in this patient previously been described as part of an allergic encephalopathy. The main disturbance was of the upper brain stem and basal ganglia, presenting as a variety of involuntary movements over the course of 6 months, followed by almost complete recovery.

Case report

A housewife, aged 36 years, was admitted to the Psychiatric Department of St George's Hospital under Dr P. B. Storey in November 1967 with an anxiety state. Symptoms, which consisted of panic attacks, fear of going out and meeting people, and palpitations, had been present since 1959 and had not responded to out-patient treatment with meprobamate and diazepam. Thyroid function studies and an electroencephalogram (EEG) were normal. She gave a history of having had a rash as a child after contact with certain metals and after having eaten shell fish, and in 1957 developed an exfoliative dermatitis while on treatment with sulphonamides.

Treatment was begun with 4-hourly dichloralphenazone 1200 mg, triclofos 500 mg and chlorpromazine 25 mg, but on the 8th day she felt unwell, had involuntary twitching of the mouth and then an oculo-gyric crisis which responded to benztropine 2 mg i.m. During the next few hours she vomited, became pyrexial and developed an erythematous maculo-papular rash which started on the face, where there was oedema of the lips, eyelids and ears, and later became confluent and spread to involve the whole skin surface. The fever rose to 105°F, and lasted 5 days, with restlessness, confusion, disorientation and hallucinations. As the fever subsided the rash began to exfoliate and she developed dysarthria

and dysphagia and became stuporous, lying inert, her eyes open, responding to visual threat but not to verbal commands or to painful stimuli. She became doubly incontinent and developed diarrhoea which persisted for 6 weeks. At this stage the patient was transferred to the Neurological Department.

Involuntary movements at the onset of the stupor consisted of intermittent conjugate oblique pendular movements of the eyes, and repetitive twitching of the mouth. Within 24 hr these eye movements were replaced by spasmodic convergence or downward gaze with lid retraction, a reaction which could be produced by palatal stimulation. Mouth twitching became bilateral, spread to involve the arms and was almost continuous, varying in amplitude and at times becoming violent. Tone in the limbs slowly increased so that 10 days later the legs were rigidly extended and the arms and hands fully and firmly flexed at every joint.

Over the following weeks the tone in the limbs and the amplitude and frequency of the tremor decreased, and, superimposed on this, coarser sudden jerking movements appeared, particularly flexion and extension of the hips, trunk and shoulders, together with bizarre facial grimacing. During this time the patient became progressively more restless until she was rarely still, constantly trying to climb out of her cot and continuously swaying backwards and forwards. She was able to obey simple commands slowly, started to swallow and after several weeks of almost continuous screaming and crying began to speak in a dysarthric fashion.

Improvement over the following months was slow. Once able to walk the patient did so almost unceasingly, and when sitting she continuously swayed to and fro, flexing her hips and knees and frequently emitting a high pitched repetitive cry. She was irritable and uncooperative, childish and uninhibited. Six months after the onset of the neurological illness she became normal both mentally and emotionally with no evidence of her long-standing anxiety state. The residual neurological abnormalities consisted of a slurring dysarthria, mild ataxia, slight terminal tremor on the finger-nose test, difficulty in

performing individual finger movements and occasional lid retraction on downward gaze. In addition, there was some fixed flexion of the fingers. This appeared to be due to tethering of tissues in the palm of the hand. Fixation had occurred when the fingers were rigidly flexed in the presence of superficial infection of the exfoliating skin. The fingers were subsequently straightened by passive stretching with serial plasters.

Investigations. During the first 2 weeks of the illness the following investigations were carried out: WBC 17,500/mm³, 83% neutrophils, 13% lymphocytes, 4% monocytes; ESR 40 mm/hr; plasma urea 61 mg/100 ml; serum electrolytes within normal limits; serum aspartate transaminase 29 units/ml (normal 0–20); serum alanine transaminase 24 units/ml (normal 0–15); other liver function tests including serum bilirubin, flocculation tests, alkaline phosphatase and protein electrophoretic strip within normal limits; CSF 4 lymphocytes/mm³, 5 mg protein/100 ml; blood and stool culture—no pathogens; complement fixation titre for mumps V and S and LCM all less than 8, and for herpes simplex 16; urine—no excess of cells, trace of protein, no porphyrins, slight excess of urobilinogen.

The blood white cell count and ESR, plasma urea, serum enzymes and the urine were normal when examinations were repeated in the course of the next few weeks, and no rise in viral antibodies was detected.

The EEG, at the onset of the stupor showed that the alpha rhythm was slowed to 7–8 cycles/sec and disturbed periodically by 2 cycles/sec waves, present on both sides equally. Ten days later similar records were disturbed by high voltage 3 cycles/sec waves associated with spikes. The changes were thought to be due to a lesion in the brain stem. One year later the records were within normal limits.

Treatment. When the rash appeared phenergan and piriton were given for 4 days, and hydrocortisone i.m. was given for 8 days after the onset of the stupor, starting at 400 mg/day.

Discussion

Although the aetiology of the encephalopathy has not been proved, there are a number of indications that it was an allergic reaction to drugs. The encephalopathy occurred in a patient who had a history of sensitivity reactions and had previously developed an exfoliative rash whilst on sulphonamides. The illness started on the 8th day of treatment with drugs to which the patient had not previously been exposed, and the neurological disturbance was preceded by a 5-day period of high fever associated with a generalized rash which later exfoliated. Rashes may accompany virus infections but they do not characteristically take the severe

form seen in this patient, nor are they usually accompanied by facial oedema; both of these features are commonly seen in allergic skin disorders. Moreover, the other systemic disturbances, the persistent diarrhoea, the transient albuminuria and elevation of plasma urea and serum enzymes, have all been described in allergic reactions.

There have been few reports of encephalopathy resulting from delayed allergic reaction to drugs and of these the case described by Cavanagh (1953) bears the closest resemblance to the present case. Cavanagh's patient developed fever, an exfoliative rash and facial oedema on the 17th day of treatment with *para*-amino salicylic acid and streptomycin, and this was followed by convulsions, coma, anuria and death. There are other reports of encephalopathy as a reaction to streptomycin (Edge, 1951) to propylthiouracil (McCormick 1950), and more commonly to sulphonamides (Fisher & Gilmour, 1939; Roseman & Aring, 1941; Scheinker, 1943; Kinlaw & McCune, 1961). In these, as with Cavanagh's case (1953), the neurological abnormality has consisted of coma, fits or increased reflexes, and in those coming to necropsy focal haemorrhagic and necrotic changes have been found predominantly in the white matter of the cerebral hemispheres. An exception to this is the case of Roseman & Aring (1941) in which the grey matter of the cortex and basal ganglia was affected histologically. In two cases, clinical evidence of disturbance of the basal ganglia has been described, but in both the signs were slight compared with the present case. Marsh (1952) described athetoid movements and weakness with fever, rash and facial oedema in a patient on streptomycin and *para*-amino salicylic acid, and Rollison, O'Brien & Good (1961) mention jerky movements resembling chorea in a patient on sulphonamides. This patient had also had for 5 months, arthralgia, a raised ESR and lupus erythematosus cells in the blood. The CNS involvement may, therefore, have been a manifestation of disseminated lupus erythematosus rather than an acute allergic reaction of the type described here. It is generally assumed that the disorder in the central nervous system results from a local antigen-antibody reaction, but the factors determining the distribution of lesions are not known.

The drugs used in the present case were: (i) triclofos, a stable ester of trichlorethol, of small molecular weight and very rarely associated with any adverse reactions; (ii) dichloralphenazone, a complex of phenazone and dichloral hydrate, of which the phenazone moiety may produce skin reactions; and (iii) chlorpromazine, a phenothiazine which may produce skin reactions as well as a number of unwanted effects on various organs, some of them occurring only in susceptible individuals. It is of interest that in the present case, although the neuro-

logical disturbances differ in their time-sequence and in their association with other manifestations of an allergic reaction, nevertheless they bear a close similarity to the well recognized non-allergic disorders of tone and involuntary movements which occur with phenothiazines. These may be classified into four groups (see Ayd, 1961; Cohen, 1956; Hunter, Earl & Thornicroft, 1964).

(1) Acute dystonia and dyskinesia affecting particularly the eyes, face, neck and arms, and occurring usually within a few days of starting the phenothiazine.

(2) Akathisia with restlessness and inability to keep still.

(3) Parkinsonian picture. The disability in Groups (2) and (3) usually starts within 3 months of starting the drug in susceptible people and the disorder is dose-dependent.

(4) Bucco-lingual dystonia, an irreversible disorder seen in elderly patients, who frequently have other brain damage, and in whom the movements start after prolonged large doses of phenothiazines.

The occurrence of these involuntary movements indicates that the phenothiazines, and particularly chlorpromazine, have a selective effect on the metabolism of the cells of the basal ganglia. Structural changes have been seen in neurones in this region after exposure to chlorpromazine, both in humans and in experimental animals (Roizin, True & Knight, 1957). The means by which chlorpromazine produces these changes is not known, although it has been suggested that it interferes with dopamine metabolism. It is not known whether the drug is concentrated in the basal ganglia. If the encephalopathy in the present case is caused by an allergic reaction to chlorpromazine, then it might be postulated that the basal ganglia had borne the brunt of the disturbance because this was the site where the allergenic chlorpromazine metabolite was concentrated.

It has been suggested (Davies, 1958) that both chlorpromazine and sulphonamides may be broken down to the same quinone ring, a structure which combines readily with protein to form a stable complex, and therefore one that is likely to be an

allergen. If this is so, then cross-sensitization between the two drugs could occur, and in this patient the severity of the reaction might be due to exposure and sensitization to a sulphonamide metabolite 10 years previously.

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