Neuroleptic malignant syndrome

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Abstract
Five patients with neuroleptic malignant syndrome (NMS) are described. The syndrome developed earlier and took longer to resolve in patients with schizophrenic disorders. Deterioration in the level of consciousness presented earlier than rigidity and fever in all five patients and was thus considered a major criterion. A significant proportion of the patients showed abnormalities of gaze. In four of the five patients spontaneous recovery occurred without the need for specific drugs.

Neuroleptic malignant syndrome (NMS) is an uncommon occasionally fatal response to neuroleptic drugs and is characterised by hyperpyrexia, muscular rigidity, autonomic dysfunction and an altered level of consciousness.1,2 The syndrome has been described as a result of increasing the dose of neuroleptic drugs within the therapeutic range, rather than as a toxic manifestation.3,4 Infrequently, withdrawal of anti-Parkinsonian medication precipitates NMS.5,6 Elevated creatinine kinase (CK) concentrations are a frequent accompaniment.7,8 Alternations in levels of consciousness have been observed as having normal levels of serum CK, involvement of ocular gaze and early onset and late resolution in schizophrenic disorders. In four patients there has been a spontaneous recovery without the use of dopamine agonists or dantrolene.

Case 1
A 25 year old male schizophrenic who had been on chlorpromazine (CPZ) for a number of years was admitted in an agitated, restless, aggressive state with excessive and inappropriate speech. Haloperidol 20 mg was administered intravenously. After an hour he became drowsy, withdrawn and unconscious. Twenty four hours later he became hyperpyrexial. Seventy two hours later he became rigid with tachycardia, tachypnoea and excessive sweating. Neurological examination showed hyperactive deep tendon reflexes with bilateral plantar extensor responses, rigidity with normal ocular and pupillary functions. All neuroleptic medications were discontinued. Diazepam 60 mg intravenously in divided doses was administered over the next 48 hours at which time he became afebrile. Alertness was regained 96 hours later. Over the next 16 days he regained his normal mental state and muscle tone, with a return of normal deep tendon reflexes and plantar responses. Subsequently CPZ was reintroduced to control his overt schizophrenic disorder. He remains essentially stable at follow up.

Case 2
A 42 year old man with a known affective disorder was admitted to hospital in an agitated restless state. CPZ 300 mg with haloperidol 9 mg, both in divided doses, was administered orally during the initial 24 hours after admission. As his mental state remained unchanged haloperidol was increased to 15 mg a day in divided doses over the next 24 hours. Seventy two hours later he progressed from drowsiness to semiconsciousness. After 96 hours he became hyperpyrexial, and rigid with conjugate gaze paresis to the left, and developed retention of urine. Diazepam 30 mg was administered intravenously in divided doses over the next 24 hours. Six days later he became afebrile and regained normal bladder control and ocular movements. Three weeks after admission CPZ was reintroduced. He has remained stable at follow up.

Case 3
This 23 year old man who had been taking CPZ and promethazine for an affective disorder was admitted in an agitated, restless and hyperkinetic state with excessive talking. Haloperidol 20 mg was administered intravenously. Forty eight hours later he became progressively drowsy and hyperpyrexial with...
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tachycardia and excess sweating. He also became rigid and experienced retention of urine. Cessation of all neuroleptic medication resulted in a gradual but total recovery of the patient within seven days of taking CPZ, promethazine and haloperidol. He was reintroduced to CPZ without adverse effects.

Case 4

A 23 year old male catatonic schizophrenic received haloperidol 20 mg intravenously to control his transient agitated restless state in addition to his daily dose of CPZ. Six hours later he became drowsy, mute and semiconscious. Twenty four hours later he became febrile with rigidity, retention of urine, tachycardia, tachypnoea, excessive sweating and a gaze paresis to the left. All neuroleptic drugs were discontinued. He became afebrile on the fifth day, regained normal muscle tone and bladder control on the tenth day after administration of haloperidol. Subsequent intake of CPZ for his schizophrenic state has been uneventful.

Case 5

This 55 year old female hypertensive schizophrenic was on multiple neuroleptics including butyrophenones. Four days before admission she became febrile, disoriented and lapsed into semiconsciousness. Within 48 hours of admission she became hyperpyrexial, developed a Parkinsonian type rigidity with tremor of all four extremities. All neuroleptic drugs were discontinued. She became afebrile six days after admission. However, her Parkinsonian rigidity and tremor continued. She was given a combination of levodopa and dopa decarboxylase inhibitor in gradually increasing doses as well as bromocryptine. She was able to walk within two weeks of admission and a gradual reduction in the dose of her anti-Parkinsonian drugs was continued at follow up. During her illness she developed renal failure with bacterial sepsicaemia which regressed completely by the time she was discharged. Blood culture showed a profuse growth of gram negative organism (E Coli). Cultures became sterile following the use of appropriate antibiotics.

Discussion

Levenson's criteria were utilised in this series for diagnosis.2 Case 5 was unusual because of the association of bacterial sepsicaemia. We would, however, like to emphasise a number of uncommon features in this group of patients. Alteration in the level of consciousness dominates all the published reports.189 Since this is consistently present in all descriptions of NMS189 and precedes all other physical findings, our experience also suggests that alteration in the level of consciousness should be considered a major criterion.2 The lowered level of consciousness may be the result of a reduced dopaminergic effect with secondary reduction in cerebral blood flow.10

In this, as well as other series, hyperpyrexia3-7,11 has been a cardinal feature. Central dopaminergic blockade probably precipitates the hyperpyrexia,8,11 whilst a direct toxic effect on skeletal muscle by phenothiazines and butyrophenones through a dopamine receptor block has been implicated.9,11 The elevation of serum creatine kinase levels supports this view.9,11 None of our patients showed an elevated creatine kinase. We would therefore conclude that direct muscle toxicity has little part to play in the production of hyperpyrexia in NMS. Instead we propose that dopamine receptor block in the hypothalamus might be the pathogenic mechanism.12-15

Dyskinesias in our patients included rigidity, opisthotonus, Parkinsonism, and tremors. None of the patients showed choreoathetoid movements described elsewhere.1468 Dopaminergic receptor blockade by phenothiazines and butyrophenones at the nigrostriatal connections explains the appearance of the dyskinetic disorder.1 We wish to emphasise the concurrence of hyperpyrexia with the peak of dyskinetic movement disorder in the course of NMS in this series. This phenomenon, in addition to the cases of NMS occurring after sudden withdrawal of dopaminergic drugs,4-6 suggests a dopaminergic receptor block at the hypothalamic, caudate and pallidal nuclei.

Various ocular abnormalities have been described as a side effect of phenothiazine and amitryptiline and infrequently as a component of NMS. These include oculogyric crises and internuclear ophthalmoplegias.143,16-19 However, to our knowledge, gaze paresis seen in two of our patients has not previously been described. Recovery from gaze paresis, with resolution of NMS, makes a structural lesion of the hemispheres or brainstem unlikely. Reversal of amitryptiline induced internuclear ophthalmoplegia by intravenous physostigmine30 suggests that mechanisms other than dopaminergic receptor blockade are also operative in the production of ocular dysfunction in NMS. Urinary incontinence has been described frequently in association with NMS,3 however, we are unable to explain the prolonged periods of urinary retention in three of our patients. Since these patients continued to exhibit this physical sign despite regaining normal conscious levels, lowered levels of consciousness cannot be the explanation.

We can find no suitable explanation for the earlier onset of NMS and its prolonged duration with a greater mortality in patients with schizophrenic disorders21,22 compared with the affective disorders. Unlike other reported instances of NMS where dantrolene and/or dopamine receptor agonists were used as therapeutic measures, these drugs were not needed except in one case. Neuroleptic malignant syndrome has been reported to have a mortality of 20%.1 All our patients recovered.

Our patients might represent different degrees of response to phenothiazines and butyrophenones. We have no reason to believe that our patients showed a different form of NMS.

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