

## SHORT REPORT

## Neuroleptic malignant syndrome and hypothyroidism

A P Moore, I A Macfarlane, L D Blumhardt

### Abstract

**Two patients with primary hypothyroidism who developed neuroleptic malignant syndrome (NMS) are described. Thyroid disease might predispose to NMS by altering brain dopamine metabolism.**

Neuroleptic malignant syndrome (NMS) may occur during treatment with neuroleptic drugs or on sudden withdrawal of levodopa. Core features include hyperthermia, muscle rigidity, altered consciousness and autonomic instability, with an elevated serum creatine kinase and peripheral blood leucocytosis.

The pathogenesis remains uncertain. NMS is not clearly related to duration of exposure to, or dosage of, neuroleptics, and does not inevitably recur on further exposure.<sup>1,2</sup> We describe two patients with primary hypothyroidism who developed NMS while taking a neuroleptic drug. Metabolic changes secondary to hypothyroidism, particularly of dopamine systems within the brain, may have predisposed them to NMS.

### Case 1

A 55 year old female presented with progressive personality change, intellectual decline and ataxia. An EEG showed diffuse theta activity and slow alpha rhythm. Her cerebrospinal fluid (CSF) contained an elevated protein concentration (1.7 g/l) but normal cell count. During investigations a paranoid psychosis developed and she was treated with several 50 mg doses of thioridazine. She then had a grand mal seizure and became increasingly drowsy. On transfer to our unit she was stuporose and pyrexial (41°C) with marked limb rigidity. A CT scan was normal, but the EEG had deteriorated with widespread delta activity. The CSF now revealed an elevated white cell count ( $50 \times 10^6/l$ , 90% lymphocytes) and total protein 1.2 g/l with a normal glucose. CSF Gram stain and cultures were negative. Muscle enzymes were grossly elevated: CPK 12,360 U/l (normal < 175), AST 288 U/l (normal 13-42) and HBD 800 U/l (normal 50-290). NMS was diagnosed and she was treated with vigorous cooling and fluid and electrolyte maintenance. Whilst the CSF cell

count was unusually high, non-specific CSF abnormalities do occur in NMS.<sup>2</sup> The total serum thyroxine was then found to be low (40 nmol/l, normal 50-150) and thyroid stimulating hormone (TSH) high (> 50 mU/l, normal < 7.4). This may explain her persistently raised CSF protein.<sup>3</sup> Treatment with oral thyroxine 0.1 mg/day was started. She recovered from the acute illness over a period of 10 days. Two months later she was clinically and biochemically euthyroid and the chronic encephalopathy had resolved.

### Case 2

A 32 year old woman had a 15 year history of an obsessional anxiety neurosis that had been treated with antidepressants and benzodiazepines. In November 1987, she became clinically and biochemically hypothyroid. Subsequently she became euthyroid on oral thyroxine 0.1 mg/day. In January 1988, agitation developed and she was treated with thioridazine, her first exposure to a neuroleptic drug. This was stopped in January 1989, when she was still clinically and biochemically euthyroid.

In March 1989, she was admitted with agitated depression. She received 50 mg thioridazine and 10 mg haloperidol. Within 24 hours she developed a pyrexia of 38.5°C, tachycardia, increasing muscle rigidity and stupor. NMS was suspected and neuroleptic drugs discontinued. The serum CPK was > 2000 IU/l, but liver function tests showed only minor abnormalities. CT brain scan was normal. Screening for infection, including CSF examination, was negative. The serum free T4 on admission had been in the low normal range, 14.4 pmol/l (NR 11-22), but the serum TSH was raised (36 IU/l). Three days after the onset of NMS the free T4 was 14.1 pmol/l and the TSH had risen to > 70 IU/l.

On transfer to our care she was pyrexial (38°C) and mute with severe generalised muscular rigidity. She was cooled and given intravenous dantrolene and thyroxine 0.1 mg/day. She improved considerably over several days and the serum CPK fell to 930 IU/l. The dantrolene was stopped and after one week she was returned to the referring hospital. Although no further neuroleptic drugs were given, over the next seven days she became

Department of  
Neurological Science,  
University of  
Liverpool, Walton  
Hospital, Liverpool  
A P Moore  
I A Macfarlane  
L D Blumhardt

Correspondence to:  
Dr A P Moore,  
Department of Neurological  
Science, Walton Hospital,  
Rice Lane, Liverpool L9  
1AE, United Kingdom.

Received 28 July 1989 and in  
revised form 25 October  
1989.

Accepted 13 November 1989

mute with cogwheel rigidity and was readmitted. The serum CPK had risen to 1580 IU/l. The serum total thyroxine was in the normal range (97 nmol/l) but the serum TSH was again considerably elevated (> 50 mU/l), indicating she had not received her thyroxine therapy in recent days. A relapse of NMS was suspected and iv dantrolene and oral thyroxine restarted. Over three weeks she gradually improved and the CPK settled to normal.

### Discussion

In NMS there is thought to be a disturbance of both hypothalamic and basal ganglia dopaminergic function. The most likely cause is dopamine receptor blockade by neuroleptic drugs,<sup>2</sup> but other factors may be involved. Organic brain syndromes may predispose to NMS<sup>1,2</sup> although a review of 60 patients found only 11 to have an identifiable brain disease or history of drug abuse before neuroleptic exposure.<sup>4</sup>

Our patients both developed NMS whilst hypothyroid. It was the first exposure to neuroleptic drugs for patient one. The second patient had previously received a neuroleptic drug but at that time she was known to be biochemically euthyroid. When she developed NMS she was mildly hypothyroid, probably because of poor compliance. A high and rising serum TSH and falling serum T4 indicate that thyroxine replacement was inadequate. Therefore, she was hypothyroid for both the initial episode of NMS and the recurrence.

Thyroid disease has not previously been linked with NMS but theoretically might be

relevant. In hypothyroid rats, dopaminergic activity is increased. Tuberoinfundibular neurons probably secrete extra dopamine<sup>5</sup> and high TSH levels increase thyrotroph dopamine receptor numbers.<sup>6</sup> Dopaminergic activity inhibits TSH release in a feedback loop. In addition, TRH may increase the sensitivity of postsynaptic dopamine receptors in the striatum and limbic forebrain.<sup>7</sup>

We suggest that the general increase in dopaminergic activity in hypothyroidism causes compensatory changes in motor control systems. If the excess dopaminergic action is then abolished by a neuroleptic drug severe rigidity could follow. Thyroid dysfunction should be excluded in all patients who develop NMS, not least because the encephalopathy of hypothyroidism might explain why neuroleptic treatment was given in the first place.

We thank Dr I R Williams for permission to include one of his patients in this paper.

- 1 Lim R. Idiopathic hypoparathyroidism presenting as the neuroleptic malignant syndrome. *Br J Hosp Med* 1989; 41:182.
- 2 Guze BH, Baxter LR. Neuroleptic malignant syndrome. *N Eng J Med* 1985;313(3):163-6.
- 3 Fishman RA. In: Weatherall DJ, Ledingham JGG, Warrel DA, eds. *Oxford Textbook of Medicine* 1988, 2nd ed. Oxford: Oxford University Press.
- 4 Caroff SN. The neuroleptic malignant syndrome. *Clin Psychiatry* 1980;41(3):79-83.
- 5 Raymond MJ, Benotto W, Lemarchand-Beraud T. The secretory activity of the tuberoinfundibular dopaminergic neurones is modulated by the thyroid status in the adult rat: consequence on prolactin secretion. *Neuroendocrinology* 1987;46:62-8.
- 6 Foord SM, Peters JR, Dieguez C, Shewring G, Hall R, Scanlon MF. TSH regulates thyrotroph responsiveness to dopamine in vitro. *Endocrinology* 1986;118:1319-26.
- 7 Funatsu KS, Inanaga K. Modulation of dopamine receptors by thyrotrophin-releasing hormone in the rat brain. *Peptides* 1987;8:319-25.