Lesson of the Week

Resolution of dyskinesia and the “on-off” phenomenon in thyrotoxic patients with Parkinson’s disease after antithyroid treatment

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Many patients with Parkinson’s disease develop complications of long term treatment with compounds containing levodopa. These complications include the “on-off” phenomenon and dyskinesia and develop after two or three years of treatment in some 15-40% of patients.1 Thyrotoxicosis has been reported in association with Parkinson’s disease in patients with severe tremor, and in three cases the tremor subsided with treatment of the endocrine disorder.2 I report two patients who developed late side effects of treatment of Parkinson’s disease which were reversed by correcting co-existing thyrotoxicosis and examining the postulated mechanism.

Symptoms and signs of thyrotoxicosis may easily be dismissed as late complications of levodopa in patients receiving this drug for Parkinson’s disease; only a high index of suspicion and a therapeutic trial of antithyroid medication will yield the correct diagnosis.

Case 1

A 66 year old woman with a seven year history of Parkinson’s disease well controlled for four years with levodopa-carbidopa (Sinemet) presented with a four month history of night terrors, depression, dyskinetic movements, and episodes of freezing typical of the “on-off” phenomenon. She admitted...
to weight loss, palpitations, and heat intolerance and to symptoms of depression with loss of appetite, early morning waking, and depressed affect.

Examination showed her to be anxious and sweaty with pronounced choreiform movements of the head and trunk. The thyroid was smoothly enlarged; the temperature and pulse was 102°F (38.8°C) with moderate rigidity of cogwheel type with bradykinesia and an intermittent pill rolling tremor. She scored 8/10 on a simple mental state questionnaire. Modification of the levothyroxine regimen (smaller, frequent doses) achieved no improvement. Thyroid function studies showed hyperthyroidism with serum total thyroxine concentration 155 nmol/L (normal 68-141), serum triiodothyronine resin uptake 1:00 (normal 0:68-1:04), serum adjusted thyroxine concentration 155 nmol/L (normal 57-124), and serum triiodothyronine value 2:7 nmol/L (normal 1:2-3:2). A 400 µg thyrotropin releasing hormone stimulation test produced an impaired response, with a thyrotropin hormone concentration of 1:3 mIU/L at zero time and 4:7 mIU/L at 20 minutes (difference 3:4, normal change >5:0). Carbamazole 10 mg three times a day was introduced and increased to 15 mg thrice daily. After two weeks the choreiform movements had improved, and when reviewed after four weeks her freezing episodes had stopped. She received a course of radioactive iodine and remained well for two years taking Sinemet, with no recurrence of the on-off phenomenon or dyskinesia.

Case 2

A 77 year old woman with a 15 year history of Parkinson's disease treated with amantadine and Sinemet was referred for assessment of dystonic head movements. She admitted to weight loss and intolerance of heat. Examination showed a thin, anxious woman with a small nodule in the right side of the thyroid, tachycardia of 130 beats/min, and constant bobbing of the head and neck to the left. She had minimal rigidity and scored 10/10 on the simple mental state questionnaire. Thyroid function studies showed hyperthyroidism, with serum total thyroxine concentration 147 nmol/L, serum triiodothyronine resin uptake 0:93, serum adjusted thyroxine concentration 147 nmol/L, and serum triiodothyronine value 3:0 nmol/L. A 200 µg thyrotropin releasing hormone stimulation test showed an absent response (thyroid stimulating hormone concentration 1:4 mIU/L at zero time, 1:3 mIU/L at 20 minutes). Carbamazole 10 mg thrice daily was begun and within four weeks her tachycardia had settled to below 100 beats/min. By review at eight weeks her head movements had disappeared, she had gained weight, and she was less anxious. Carbamazole was reduced to 5 mg three times a day and she remained clinically euthyroid. After three months a repeat thyrotropin releasing hormone stimulation test showed an improved but still impaired response (thyroid stimulating hormone 3:6 mIU/L at zero time, 5:3 mIU/L at 20 minutes, difference 1:7).

Discussion

Thyrotoxicosis may be difficult to diagnose in patients with Parkinson's disease because symptoms of sweating, weight loss, and irritability may be attributed to their extrapyramidal disease or drugs or to depression, which occurs in 40% of these patients at some time in their disease. It has been reported that weight loss is the only common symptom in elderly patients with thyrotoxicosis and occurs in three quarters or more, while the classical signs of thyrotoxicosis (weight loss, agitation, exophthalmos, tremor, and tachycardia) may be absent in the elderly. The withdrawn appearance of a patient with "apathetic thyrotoxicosis" may be similar to that of a patient with Parkinson's disease, especially in the elderly, who tend to have more akenisia and rigidity than tremor.

Our first patient complained of symptoms typical of patients who have been taking levodopa for several years, with choreiform movements and on-off phenomenon, both of which suggest late complications of treatment. The psychiatric disturbance led to her being admitted initially to the psychogeriatric service, with later transfer to the geriatric assessment unit, where the correct diagnosis was made. In both cases the impaired response to the thyrotropin releasing hormone stimulation test might have been discounted because of levodopa treatment, and a therapeutic trial of carbachol was the only way to resolve the diagnostic dilemma.

Response to the thyrotropin releasing hormone stimulation test improved in patients taking Sinemet, who had a carbachol skin test which was not in those not taking the drug; this may, however, be an artefact, patients with more severe disease needing levodopa and having a poor response owing to their disease rather than the drug. Levodopa suppresses release of prolactin from isolated pituitary cells stimulated by thyrotropin releasing hormone and it is assumed that this effect holds for the release of thyroid stimulating hormone. This makes the thyrotropin releasing hormone test less discriminatory in patients taking levodopa. As an additional problem, the response to the thyrotropin releasing hormone stimulation test may be impaired in up to a quarter of healthy elderly people over 80 not taking any drugs (unpublished observation). Hence a high index of suspicion on clinical grounds, a therapeutic trial of antithyroid medication, and monitoring of the clinical response is the only way of deciding whether the diagnosis is correct.

The on-off phenomenon and dyskinesia may be induced by overdosage with levodopa, and chorea has been reported as a manifestation of hyperthyroidism. It is tempting to suggest that the excess triiodothyronine and the postsynaptic receptors to dopamine and induced the abnormal movements which were abolished by correct treatment.

In conclusion, these two cases show the difficulties in diagnosing thyrotoxicosis in patients receiving levodopa for Parkinson's disease and that restoring a euthyroid state may ameliorate some of the late complications of levodopa which may develop when these conditions coexist.

References


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Is there any reason to suppose that occasional local use of an oestrogen cream (Premarin vaginal cream) for postmenopausal atrophic vaginitis carries any increased risk of thromboembolism?

One gram of Premarin vaginal cream contains 0-625 mg of conjugated oestrogens, and a standard daily dose can increase plasma oestradiol to follicular phase levels, even though systemic absorption may be less with vaginal than with oral preparations. Conjugated oestrogen treatment after the menopause has a variety of biochemical effects that could theoretically be either adverse or beneficial. For example, the effects on plasma lipids include an increase in high density lipoprotein cholesterol (which might protect against cardiovascular disease), and the effects on the clotting mechanism include a reduction in the main coagulation inhibitor antithrombin III (which could predispose to thromboembolism).

Nevertheless, epidemiological studies have shown no convincing link between postmenopausal oestrogen use and cardiovascular disease or thromboembolism. 1-12—JAMES OWEN DRIFTE, senior lecturer in obstetrics and gynaecology, Leicester.