Thyroid dysfunction can precipitate a multitude of clinical symptoms and signs. Both hyperthyroidism and hypothyroidism can manifest with neurological abnormalities. Hyperthyroidism can present with a variety of neurological syndromes including chorea and myopathy, and less commonly with peripheral neuropathies.1 Cerebellar ataxia has been typically recognized in association with hypothyroidism, but not hyperthyroidism. Here we report a case of a young male patient who presented with florid symptoms and signs of cerebellar syndrome with no clinical evidence of thyrotoxicosis. Biochemical hyperthyroidism was confirmed in the patient, and its treatment resulted in the complete resolution of the cerebellar syndrome. Only 1 case of the association of cerebellar signs was reported in a patient with thyrotoxicosis, albeit in a different clinical and biochemical context (Aberg et al 1976).2

**CASE**

A 16-year-old keen footballer presented to the emergency department one evening in September 2011, following an episode of unusual behavior on the football pitch. The patient was unable to recall the events clearly, but he described a sudden onset of “dizziness and disorientation.” He denied any loss of consciousness. His teammates described him to be staggering across the pitch, appearing “drunk,” though no collapse was wit-
nessed. An ambulance was called, and the patient complained of a further headache en route to the local hospital, where he was admitted to the medical on-call team. This episode occurred a week after having attended the general medical outpatient clinic. Referral was initiated by his primary care physician when he was approached by the patient a month earlier, with ongoing symptoms of "unsteadiness" and " clumsiness." The patient claimed to have awoken one morning, feeling "unsteady." He initially disregarded his symptoms; however, his mother had become increasingly concerned when he started to bump into people. At this consultation, which occurred a few days prior to his presentation, the patient was noted to be mildly ataxic, with a cerebellar tremor. At this time, a computed tomography (CT) of head was organized, as there was a concern of posterior fossa space occupying the lesion. Routine bloods, including thyroid function tests, were also carried out at this time. A few days later, this returned showing a suppressed thyroid stimulating hormone (TSH) (<0.03 mu/L) and high free T4 of 37 pmol/L (normal reference range 12-27 pmol/L). Here, the patient was contacted to start on carbimazole (methimazole), though admittedly he did not start the drug until the day of presentation to the hospital.

On admission to the emergency department, he was fully conscious and orientated, with a resting radial pulse of 80/min in normal sinus rhythm and a normal blood pressure with no evidence of postural drop. Chest and abdominal examination were normal. No visible goitre was observed; however, the palpation of the neck suggested mild thyroid enlargement. On neurological assessment, he was noted to have gross cerebellar signs, marked more on the left than on the right. Reflexes were globally brisk. The evidence of ataxia was confirmed, and a full course of 18 months carbimazole was planned. The patient remained euthyroid on the maintenance dose of carbimazole with no evidence of the recurrence of his cerebellar syndrome after 7 months of follow-up at the Endocrine Clinic.

Laboratory tests revealed normal full blood count with normal hematological indices, urea, creatinine, electrolytes, liver function tests, bone profile, parathyroid hormone, vitamin D3, vitamin B12, and folate, and clotting profile. Repeat TFTs confirmed biochemical hyperthyroidism with suppressed TSH (<0.03 mU/L) and high free T4 (41 pmol/L). Immunological tests showed weakly positive anti-nuclear antibodies (ANA) in a titer of 1:160 but showed negative extractable nuclear antigens screen that included anti-Ro, La, Sm, Scl-70, Jo-1, and centromere-Ab. Other immunological tests, including lupus anticoagulants (anticardiolipin antibodies) (both immunoglobulin G [IgG] and IgM), anti-neutrophil cytoplasmic antibody, and double-stranded DNA (dsDNA), were all negative.

The patient underwent magnetic resonance imaging followed by magnetic resonance angiography, none of which showed any parenchymal brain abnormalities or evidence of vascular occlusion or aneurysm in his cerebral circulation. Lumbar puncture revealed clear cerebrospinal fluid with normal opening pressure, and laboratory analysis showed normal glucose, protein, white blood cells, red blood cells and no evidence of xanthochromia. Neck ultrasonography reported a diffusely inhomogeneous echotexture of a moderately enlarged thyroid involving both lobes with increased blood flow on Doppler color imaging. This suggested a diffusely inflamed thyroid. The thyroid radioisotope scan showed that "the uptake of technetium-99 18 minutes after injection was 2.5%" (normal range approx. 1%-2%), in keeping with primary thyrotoxicosis. Thyroid autoantibodies, including thyroid peroxidase antibodies (anti-TPO), elevated to a level of 532 IU/mL (normal <50 IU/mL), but the TSH receptor antibody (TRAb) decreased and became negative. The patient was started on carbimazole 40 mg daily, and he clinically improved dramatically over the course of 7 days, with only subtle clinical signs at the time of discharge. To complete the investigation, an electroencephalogram was arranged to rule out any possible seizure activity to explain the unusual events precipitating presentation, and this also came back reassuringly normal.

The subsequent review in the outpatient clinic 6 weeks following discharge, with repeat biochemistry, showed a free T4 within the normal range, and the clinical examination showed subtle ataxia, which demonstrated only on tandem gait. At the 3 months' follow-up, the complete resolution of neurological abnormalities was confirmed, and a full course of 18 months carbimazole was planned. The patient remained euthyroid on the maintenance dose of carbimazole with no evidence of the recurrence of his cerebellar syndrome after 7 months of follow-up at the Endocrine Clinic.

**DISCUSSION**

In the historical pre-context, the first suggestion that there may be a functional relationship between the thyroid gland and the brain was made by the polymath British physician, Dr Caleb Hellier Parry, who first described exophthalmic goiter in 1786 well ahead of Robert Graves to the extent that Osler and others suggested to rename the condition as "Parry Disease." In some of his papers, which were published posthumously by his son, Parry postulated that the thyroid gland functions as a "vascular shunt" protecting the brain from sudden increase in blood flow. Kudrjavcev,
in his treatise on neurological complications of thyroid dysfunction, he referred to the "awareness of the role of thyroid hormones in maintaining nervous system integrity." He stopped short, however, of understanding the cellular and biochemical mechanisms by which an excess or deficit of thyroid hormone produces neurological symptoms. On the contrary, hypothyroidism is a common medical condition among the general population. Here, a variety of central and peripheral nervous system features are common by association. These range from myopathy or peripheral neuropathies, to the more rare features of altered mental status and cardiovascular collapse associated with myxedema coma. Cognitive impairment and ataxia are well recognized features in association with hypothyroidism. However, cognitive impairment is also recognized in hyperthyroidism. Patients with thyrotoxicosis may experience behavioral personality change (thyroid apathy). Other manifestations are more common, including tremors, anxiety, restlessness, irritability, and emotional liability, which are primarily related to the sensitization of the sympatho-adrenal system by the excess circulating thyroid hormones. Seizures may accompany the rare "thyrotoxic encephalopathy," and less-recognized clinical neurological correlates include pyramidal tract signs and hyper-reflexia. Much rarer neurological phenomena of hyperthyroidism include chorea, myoclonus, and embolic events related to arrhythmias and peripheral neuropathies. Some other conditions were strongly associated with autoimmune hyperthyroidism including myasthenia gravis and thyrotoxic periodic paralysis. The latter has special preponderance for certain ethnic groups.

From the abundance of neurological sequelae mentioned above, it is apparent that some associations occur more often than others; hence, we have the stereotypical image of the agitated, tremulous, thyrotoxic patient, in comparison to the lethargic, depressed patient having hypothyroid. Ataxia, incoordination, and Rombergism are well documented in combination with hypothyroidism in the current available literature; however, there is little documentation of association with hyperthyroidism. Aberg et al described the case of a 50-year-old gentleman, who was first admitted with "progressive nervousness, tiredness, sweating, and weight loss," and was found to be thyrotoxic. He underwent a subtotal bilateral thyroidectomy and remained well for a further 10 years. The same patient then became unwell in 1973, with nausea and vomiting associated with weight loss. On this occasion, there was also notable "increasing disturbance of balance, and obvious speech difficulties." He was admitted at this time emaciated in appearance, pyrexial, ataxic, and dysarthric, with the clinical evidence of exophthalmos. Opsoclonus was accompanied with marked appendicular ataxia in all 4 extremities. Several consequent admissions occurred, with further cerebellar signs on examination, each in the context of sepsis. Dramatic response was seen with steroids. Antibody titers were carried out in an attempt to prove the autoimmune pathogenesis, showing positivity of cytoplasmic thyroid antigen, in addition to antibodies against mitochondria and kidney tubules. It was noted that very low levels of complements were associated, and it was felt these findings were compatible with the continued subclinical immunological activity. The paper then postulated that 1 or more antibodies may target different organs, including the thyroid and the cerebellum. The case of Aberg et al (1976) did not have frank thyrotoxicosis at the time of observing the neurological syndrome, and the authors postulated its relationship solely on the basis of the immunological perturbation.

Interestingly, the only antibodies that were shown to be positive in our patient were anti-TPO and (weakly positive) ANA. Steroids were not trialled in our patient and symptoms resolved with the treatment of thyrotoxicosis. The hypothesis of antibodies targeting more than 1 organ may well be relevant to our case. In contrast to the case of Aberg et al (1976), our patient was well, with no evidence of concurrent sepsis. Unusually, there was no evidence of typical clinical features of thyrotoxicosis in the patient we described except cerebellar signs, suggesting that the cerebellum may well have been a target for any active autoimmune process.

In contrast to the autoimmune hypothesis, the perturbation of cerebral microvascular component may be an attractive alternative hypothesis. Park et al described the reversible radiological changes seen in cerebellum, white matter, and corpus callosum, during diffusion-weighted imaging of a patient with thyrotoxic encephalopathy. Their theory was that of alternation of regional brain metabolism in hyperthyroidism. In particular, a general increase in cerebral blood flow was seen, but the posterior circulation regions were found to be decreased in both metabolism and perfusion. We may argue that in our patient, changes in cerebral blood flow may also be explanatory of both the patient’s neurological signs and events leading to his presentation. Autoimmune thyroid disease has been shown to be associated with some abnormalities of microcirculation. Abnormalities of nail fold capillary blood flow velocity (a surrogate of microvascular perturbation) in patients with both hypothyroidism and hyperthyroidism have been reported (Pazos-Moura et al 1998).

Furthermore, et al. using the electron microscopy tech-
nique in a biopsy study, Marquez et al (2001) documented significant microvascular abnormalities including lamination and thickening of basement membrane, progressive luminal occlusion, mononuclear and mast cell infiltrates, pericyte capillary degeneration, and endothelial cell proliferation in patients with autoimmune thyroid disease. Therefore, a plausible mechanism in our patient may involve microvascular abnormalities triggering the syndrome, which resolved following normalization of metabolic perturbations. Why his neurological deficit were only confined to the cerebellar components is not clear. Furthermore, thyrotoxicosis has been associated with unusual cerebral thrombosis in the aftermath of increased hypercoagulability and has been associated with unusual cerebral thrombosis.16 Silburn et al. (1996) reported a case of a young female patient with an encephalitic picture that was attributed to cerebral venous thrombosis possibly triggered by thyrotoxicosis.17 Thyrotoxicosis was shown to predispose to cerebral thrombosis via factor VIII–mediated hypercoagulability.18 Farid et al (1976) studied coagulation and fibrinolysis in thyroid disease, and they reported increase in factor VIII levels in patients with thyrotoxicosis.19 Our patient “did neither have atrial fibrillation nor there was any evidence of cerebellar thrombosis/occlusion on imaging. But such mechanism could well be playing apart in the context of the microvascular changes, which resolved following treatment.

It will be interesting to see, if the clinical picture already described were also to return in the possible circumstance of relapsed thyrotoxicosis. This report summarizes the unusual coincidence of “cerebellarism” and thyrotoxicosis in a 16-year-old male. Given the complete resolution of clinical signs and lack of alternative explanation, we can only presume the association of the two. The underlying mechanism can only be speculative at this stage.

REFERENCES

1. Rubin DI. 2011 Neurological manifestations of hypothyroidism. In: Aminoff MJ, Ross DS (eds) Up-To-Date. UpToDate, Waltham.
2. Aberg HE, Herbai GL, Westerberg C-E 1976 Recurrent and reversible cerebellar ataxia with concomitant episodes of hyperthyroidism: a new autoimmune syndrome. Acta Medica Scandinavica 199:331-334.
3. Hull G 1998 Caleb Hillier Parry 1755-1822: a notable provincial physician. Journal of the Royal Society of Medicine 91:335-338.
4. Parry CH. 1825 Collections from the Unpublished Medical Writings of the Late Caleb Hillier Parry. Underwood, London.
5. Kudrjavcev T. 1978 Neurologic Complications of Thyroid Dysfunction. Advances in Neurology 19:619-635.
6. Rubin DI. 2012 Neurologic manifestations of hyperthyroidism and Graves’ disease. In: Aminoff MJ, Ross DS (eds) Up-To-Date. UpToDate, Waltham.
7. Okinaka S, Shizume K, lino S, et al. 1957 The association of periodic paralysis and hyperthyroidism in Japan. Journal of Clinical Endocrinology & Metabolism 17:1454-9.
8. Blume W, Grabow JD 1969 The “cerebellar” signs of myxedema. Diseases of the Nervous System 30:55-57.
9. Park MH, Ryu JK, Seo JA. 2007 Reversible splenial abnormality in thyrotoxic encephalopathy: European Journal of Neurology 14:23-24.
10. Sensenbach W, Madison L, Eisenberg S, Ochs L. 1954 The cerebral circulation and metabolism in hyperthyroidism and myxedema. Journal of Clinical Investigation 33:1434-1440.
11. Fukui T, Hasegawa Y, Takenaka H. 2001 Hyperthyroid dementia: clinicoradiological findings and response to treatment. Journal of the Neurological Sciences 194:61-68.
12. Pazo-Moura CC, Moura EG, Breitenbach MM, Bouskela E 1998 Nailfold capillaroscopy in hyperthyroidism and hyperthyroidism: blood flow velocity during rest and postocclusive reactive hyperemia. Angiology 49:471-474.
13. Marquez A, Finol HJ, De Blanco MC, Adjoumian H, Pulido-Mendez M 2001 Skeletal muscle microvascular alterations in euthyroid and hyperthyroid patients with autoimmune thyroid disease. Journal of submicroscopic cytology and pathology 33:425-432.
14. Ra CS, Lui CC, Liang CL, Chen HJ, Kuo YL, Chen WF 2001 Superior sagittal sinus thrombosis induced by thyrotoxicosis. Case report. Journal of neurosurgery 94:130-132.
15. Siegert CE, Smelt AH, de Bruin TW 1995 Superior sagittal sinus thrombosis and thyrotoxicosis. Possible association in two cases. Stroke, a journal of cerebral circulation 26:496-497.
16. Lodha A, Haran M, Frankel R, Shan I 2009 Thyrotoxicosis causing arterial and venous thrombosis. The American journal of the medical sciences 338:428.
17. Silburn PA, Sandstorm PA, Staples C, Mowat P, Boyle RS 1998 Deep cerebral venous thrombosis presenting as an encephalitic illness. Postgraduate medical journal 72:395-397.
18. Verberne HJ, Fliers E, Prummel MF, Stam J, Brandjes DP, Wiersinga WM 2000 Thyrotoxicosis as a predisposing factor for cerebral venous thrombosis. Thyroid: official journal of the American Thyroid Association 10:607-610.
19. Farid NA, Griffiths BL, Collins JR, Marshall WH, Ingram DV 1976 Blood coagulation and fibrinolysis in thyroid disease. Thrombosis and haemostasis 35:415-422.