Rising Serum Thyroxine Levels and Chorea in Graves’ Disease

abstract

A 15-year-old girl presented with chorea as a first sign of Graves’ hyperthyroidism. Chorea abated with antithyroid drug treatment and reappeared when hyperthyroidism recurred but not when thyrotropin receptor antibodies increased after administration of 131I. Therefore, chorea in this patient is associated with hyperthyroxinemia and not with autoantibodies. *Pediatrics* 2013;131:e616–e619

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KEY WORDS

hyperthyroidism, movement disorder, bone marrow transplant, sickle cell disease

ABBREVIATIONS

BMT—bone marrow transplant
fT4—free thyroxine
TSI—thyroid-stimulating immunoglobulin

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Common neurologic manifestations of hyperthyroidism are attention deficit and tremor. Although rarely, chorea and athetosis can also be associated with this endocrine disease.1–5 We report on an adolescent girl in whom chorea was the first manifestation of hyperthyroidism, both at the time of initial diagnosis and when hyperthyroidism recurred.

**PATIENT PRESENTATION**

A 15-year-old girl was hospitalized after a series of falls over the month preceding admission. Her past medical history was notable for severe sickle cell disease diagnosed during the neonatal period and which required many hospitalizations for vaso-occlusive crises and infectious diseases. At age 12 years, given the severity of her underlying condition, she underwent an allogenic bone marrow transplant (BMT) after conditioning with busulfan, cyclophosphamide, and antithymocyte globulin. The immediate follow-up after BMT was event-free except for a transient episode of blindness of unknown origin.

An MRI scan at that time did not show any sign of ischemic lesions. At age 13 years, she was diagnosed with premature ovarian failure, secondary to high-dose alkylating chemotherapy. She was treated with increasing doses of estrogens and then with an oral contraceptive. The other endocrine functions were normal at that time; specifically, thyrotropin was 1.24 mU/L (normal range \(N = 0.1–6.2\)). At age 15 years, she presented with episodes of falling up to 10 times a day. The crises were described as limb stiffness followed by uncoordinated movements that preceded the fall. There was neither loss of consciousness nor urinary or fecal incontinence. She was not taking any medications except for the oral contraceptive. Initially, the neurologic manifestations were treated as convulsive episodes with an antiepileptic drug (clobazam).

Because of a lack of improvement in symptoms after 2 weeks, the patient was hospitalized for a neurologic evaluation. On admission, she weighed 74.4 kg (stable over the last months), and her vital signs were as follows: a heart rate of 90 beats per minute, blood pressure of 126/66 mm Hg, and a temperature of 37.3°C. During her stay, several episodes were observed and described as choreiform movements by neurologists. A repeat MRI scan showed a normal brain parenchyma with no evidence of vascular thrombosis, acute ischemic lesion, or structural abnormalities in the basal ganglia. A video EEG showed several events of choreiform and dystonic movements without a stereotyped pattern and, more importantly, without any epileptic activity on simultaneous EEG recording. The infectious and inflammatory screening as well as routine biochemistry remained noncontributory. Urinary human chorionic gonadotrophin was undetectable. Cardiac evaluation with electrocardiogram and Holter monitoring did not show any dysrhythmia. Finally, the neuro-ophthalmic examination remained normal. Given that no etiology was found to explain the neurologic manifestations, a psychiatric evaluation was proposed, and the patient was discharged from the hospital with a prescription of citalopram.

Two weeks later, her annual endocrine screening revealed hyperthyroidism (free thyroxine \(fT_4\): 44.9 pmol/L \(N = 4.7–11.6\); total triiodothyronine: 6.0 nmol/L \(N = 2.1–3.3\); antibodies to antithyroidperoxidase 720 \(N = 0–34\); antibodies to thyroglobulin <20 \(N = 0–39\); and antibodies to the thyrotropin receptor \((\text{thyroid-stimulating immunoglobulins (TSlis)}): 108.8 U/L \{\text{negative} <9\}). The 24-hour thyroid \(131^{1}\) uptake was 75.2%, which was also compatible with Graves’ disease. The girl was treated with a block-replace regimen (methimazole first, then methimazole plus levothyroxine), and the choreiform movements disappeared after normalization of thyroid function.

Two years later, because of negative TSlis and normal thyroid function, it was decided to stop treatment. After 2 months, chorea recurred, as did hyperthyroidism (thyrotropin: 0.01 mU/L; \(fT_4\): 46.2 pmol/L; total triiodothyronine: 5.6 nmol/L) and TSlis increased (47.7 U/L) (Fig 1). The association methimazole/levothyroxine was reintroduced, and we observed, for a second time, resolution of neurologic manifestations, normalization of \(fT_4\) levels, and disappearance of TSlis. In the meantime, we decided on definitive treatment with \(131^{1}\) (6.5 mCi orally) followed by daily levothyroxine replacement. Thereafter, \(fT_4\) levels remained normal, and no further chorea episode was reported, although TSlis increased again just after \(131^{1}\) treatment (to 81.7 U/L) (Fig 1).

**DISCUSSION**

This case reveals that chorea can be the first manifestation of hyperthyroidism.1–5 We excluded the most frequent causes of acquired chorea in the context of the patient’s underlying medical history, such as infectious diseases (meningitis or encephalitis caused by viral, bacterial, or fungal infections), medication intake, autoimmune and inflammatory diseases, hypoxic-ischemic lesions, chorea gravidarum, disorders of electrolyte or glucose balance, and...
metabolic or neurodegenerative diseases. The final diagnosis was delayed probably because of lack of other symptoms suggestive of hyperthyroidism in a patient with a complex medical history. Indeed, this adolescent girl underwent BMT for sickle cell disease, a procedure and a condition that carry a high risk of neurologic complications. However, autoimmune hyper- and hypothyroidism post-BMT are not rare, and hyperthyroidism should be excluded in any patient with chorea.

Oral contraceptives can also be potentially responsible for chorea. However, the clinical evolution of our patient does not support this link, because symptoms appeared 2 years after starting treatment of ovarian failure, while they were temporally associated with 2 episodes of hyperthyroidism (Fig 1).

The physiopathologic mechanisms of chorea in the context of hyperthyroidism are not precisely known. This neurologic manifestation seems to be related directly to hyperthyroxinemia and not to autoimmunity, although autoimmune mechanisms have been evoked in chorea associated with systemic lupus erythematosus, primary antiphospholipid antibody syndrome, and Hashimoto thyroiditis. Patients have also been described with chorea in a context of hyperthyroidism of nonimmune or iatrogenic origin, or at initiation of thyroxine therapy in severe hypothyroidism. This finding supports the hypothesis that increasing thyroxine levels, rather than autoimmunity, are responsible for the appearance of choreiform movements. In our patient, the evolution of the levels of fT4 and TSIs shows that chorea occurred when fT4 increased but not when TSIs alone increased after ¹³¹I treatment (Fig 1).

Hyperthyroxinemia seems to increase dopaminergic receptor sensitivity, particularly in the corpus striatum. Moreover, dopamine antagonists have already been used to control chorea in patients with hyperthyroidism. In our case, the use of citalopram, a selective serotonin reuptake inhibitor that also upregulates dopamine D2 receptor gene expression, neither improved nor worsened the chorea.

CONCLUSIONS

Our observations strongly suggest that chorea is related to hyperthyroxinemia rather than to autoantibodies. Moreover, although chorea remains a rare symptom of hyperthyroidism, physicians should exclude this metabolic disorder in all patients who present with chorea.

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