Onset of Reversible Flaccid Quadriplegia during Treatment of Thyrotoxic Crisis

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Abstract

Two unrelated women were hospitalized for thyrotoxic crisis complicated by multiple organ failure. Both patients were treated with antithyroid drugs and hydrocortisone, as well as insulin for hyperglycemia, and under went mechanical ventilation with sedation. Flaccid quadriplegia became apparent after each patient completely recovered their level of consciousness once sedation was discontinued on days 6 and 15, respectively. Three to six months of rehabilitation was required for the muscle strength to fully improve in both cases. Thyrotoxicosis in addition to critical illness polyneuromyopathy and the administration of glucocorticoid therapy may have contributed to the onset of quadriplegia in these two cases. Flaccid quadriplegia is one of the serious neuromuscular conditions experienced during the treatment of thyrotoxic crisis.

Key words: thyrotoxic crisis, hyperthyroidism, myopathy, glucocorticoid, critical illness myopathy, critical illness polyneuropathy

Case Reports

Case 1 (Fig. 1)

A 46-year-old emaciated Japanese woman was hospitalized for vomiting and diarrhea. She had been diagnosed with Graves’ hyperthyroidism six years previously and prescribed methimazole (MMI). However, six months prior to the current presentation, she had discontinued the MMI against medical advice and consequently lost 7 kg in weight. She had also been previously diagnosed with a gastric ulcer and treated for Helicobacter pylori eradication. Her family and life history was unremarkable. On admission, the patient was 157 cm tall and weighed 32 kg [body mass index (BMI): 13.0 kg/m²]. She was conscious and alert, with a blood pressure of 130/70 mmHg, an irregular pulse of 100 beats/min (bpm) and a temperature of 37.5°C. There was no evidence of exophthalmos. A diffuse goiter was palpable, without bruits. The heart, lungs and abdomen were unremarkable on a physical examination, and periph-
general edema was absent. A neurological examination revealed no abnormalities, except for finger tremors and a brisk relaxation phase in the Achilles tendon reflex. The serum free thyroxine (FT4) and triiodothyronine (FT3) levels were markedly elevated at >8.0 ng/dL and >25.0 pg/mL, respectively, while the serum thyrotropin (TSH) level was suppressed at 0.03 μIU/mL. The titers of TSH-binding inhibitor immunoglobulin (TBII) and thyroid-stimulating antibodies (TSAbs) were 65% (normal range: <15%) and 416% (normal range: <180%), respectively. The findings of chest radiographs were normal [cardiothoracic ratio (CTR): 47%]; however, electrocardiography revealed atrial fibrillation (heart rate: 120 bpm).

Based on these findings, exacerbation of Graves’ hyperthyroidism was diagnosed, and treatment with oral MMI at a dose of 15 mg/day was initiated. However, on the second day of hospitalization, the patient lost consciousness and went into shock. She was immediately intubated and mechanically ventilated under sedation. Nevertheless, she subsequently developed aspiration pneumonia and exhibited atrial fibrillation with worsened tachycardia (heart rate: 150-170 bpm). She was therefore diagnosed with thyrotoxic crisis (2), and treatment with propylthiouracil (PTU) at a dose of 800 mg/day (200 mg four times daily), potassium iodide (KI) at a dose of 200 mg/day (50 mg four times daily) and hydrocortisone was commenced. Hydrocortisone was initially administered intravenously at a dose of 400 mg/day (100 mg four times daily) for eight days, followed by 300 mg/day (75 mg four times daily) for three days, then gradually discontinued over 12 days (for a total of 23 days of administration). Hematemesis was also induced by the active gastric ulcer, and the patient received blood transfusions and a proton pump inhibitor as well as endoscopic hemostasis. Unfortunately, disseminated intravascular coagulation (DIC) and hyperglycemia were detected shortly thereafter, necessitating treatment with gabexatemesilate and insulin, respectively. The patient also developed severe liver injury associated with jaundice; however, these symptoms gradually subsided (peak serum total bilirubin: 4.0 mg/dL prior to ileal perforation).

On day 6, sedation was discontinued, and the patient completely regained consciousness. Nevertheless, severe flaccid quadriplegia was apparent, and she scored 1/5 on manual muscle testing of the extremities. In addition, although she was able to blink and maintained an almost full range of eye movement in all directions, deep tendon reflexes were absent in the extremities, with preserved superficial sensation. On day 8, the nerve conduction velocities in the median nerves were found to be normal (motor nerve conduction velocity: 54.4 m/s, left 58.2 m/s; sensory nerve conduction velocity: right 61.2 m/s, left 68.2 m/s), and the patient’s muscle strength gradually recovered (manual muscle testing of the extremities: 2-3/5). However, on day 20, she developed abdominal pain and fever due to the occurrence of ileal perforation 30 cm orally from the distal end. Emergency celiotomy was subsequently performed, and the perforated part of the ileum was resected. A histopathologic examination of the resected ileum revealed microthrombi at the site of perforation, likely secondary to the previous episode of DIC. The patient’s muscle strength again deteriorated (manual muscle testing of the extremities on day 28: 1-2/5) and she required prolonged ventilatory

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**Figure 1. Clinical course (Case 1)**

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support due to respiratory muscle weakness; she was weaned off the ventilator on day 50. There were no clinically significant electrolyte imbalances associated with the muscle weakness during hospitalization. The patient’s muscle strength gradually and fully recovered over six months of rehabilitation, and she was discharged with a full ambulatory status eight months after admission.

**Case 2 (Fig. 2)**

A 47-year-old Japanese woman was admitted for dyspnea and diagnosed with New York Heart Association class IV heart failure. She reported the onset of palpitations, coughing and a slight fever three days previously. Four months earlier, she had been diagnosed with type 2 diabetes mellitus; however, her family and life history was unremarkable.

On the initial physical examination, the patient was 153 cm tall and weighed 57 kg (BMI 24.3 kg/m²). In addition, although she was conscious and restless, she was not alert (Japan Coma Scale 1), with a blood pressure of 108/73 mmHg, irregular pulse of 190-200 bpm and body temperature of 37.0°C. Mild exophthalmos was observed, and a diffuse goiter was palpable. There were no pulmonary abnormalities; however, hepatomegaly was detected. Pitting edema was noted in the lower legs. Furthermore, neurological examinations revealed no abnormalities, except for finger tremors and a brisk relaxation phase in the Achilles tendon reflex. The serum FT4 and FT3 levels were markedly elevated at 7.4 ng/dL and 24.9 pg/mL, respectively, whereas the serum TSH level was suppressed at <0.01 μIU/mL. The TBII and TSAbs titers were 68% and 388%, respectively, while the HbA1c level was 6.4%. The patient exhibited liver injury associated with jaundice and rhabdomyolysis, with serum total bilirubin and creatine phosphokinase (CPK) levels of 2.9 mg/dL and 789 IU/L, respectively. Chest radiographs revealed cardiomegaly (CTR: 69%) and bilateral pleural effusion, while electrocardiography disclosed atrial fibrillation (heart rate: 170-230 bpm).

Based on these findings, the patient was diagnosed with thyrotoxic crisis (2). On day 1 of hospitalization, she developed cardiogenic shock and was subsequently intubated and placed on mechanical ventilation and percutaneous cardiopulmonary support (PCPS) with sedation, including the administration of MMI (160 mg/day, 40 mg four times daily), KI (150 mg/day, once daily), hydrocortisone and insulin for hyperglycemia. The hydrocortisone was initially administered intravenously at a dose of 400 mg/day (100 mg four times daily) for five days, followed by 300 mg/day intravenously (100 mg three times daily) for three days, then gradually discontinued over seven days (for a total of 15 days of administration). Thereafter, the patient’s liver injury with associated jaundice and rhabdomyolysis worsened (peak serum total bilirubin: 8.1 mg/dL and peak serum CPK: 11,445 IU/L on day 4), and, on day 3, she underwent plasma exchange and received heparin for DIC. On day 4, she developed melena, and hemorrhagic duodenal and gastric ulcers were identified. A proton pump inhibitor was administered, and the hemorrhagic duodenal ulcer was treated with endoscopic hemostasis. The severe liver injury, jaundice and rhabdomyolysis gradually subsided, and the PCPS was discontinued on day 6.

On day 15, the sedation was discontinued, and the patient was weaned off the ventilator; however, severe flaccid quad-
Quadriplegia was apparent in association with alert consciousness. The manual muscle testing score for the extremities was 0/5, although the patient was able to blink and demonstrated unlimited eye movement in all directions. Furthermore, deep tendon reflexes were absent, while superficial sensation was preserved. On day 17, the nerve conduction velocities in the median nerves were slightly reduced (sensory nerve conduction velocity: right 58.5 m/s, left 51.4 m/s); however, the cerebrospinal fluid was normal and cervical MRI showed no abnormalities. In addition, a head MRI scan performed on day 20 was normal. Thereafter, the patient’s muscle strength gradually recovered. There were no clinically significant electrolyte imbalances associated with the muscle weakness during hospitalization. The patient’s paralysis completely resolved after three months of rehabilitation, and she was discharged with a full ambulatory status four months after admission.

Discussion

The two patients described in this report developed reversible flaccid quadriplegia during treatment for thyrotoxic crisis complicated by multiple organ failure. Both patients were mechanically ventilated under sedation, and flaccid quadriplegia became apparent under conditions of alert consciousness after discontinuing sedation on days 6 and 15, respectively. Manual muscle testing of the extremities yielded scores of 0-1/5 in both cases, and deep tendon reflexes were absent during the acute stage. However, eye movement remained essentially intact, and superficial sensation was preserved despite the above motor impairments. Both patients were severely thyrotoxic, with extremely elevated serum thyroid hormone levels, and their thyrotoxic crisis was treated with antithyroid drugs, inorganic iodide and hydrocortisone, as well as plasmapheresis in Case 2. In addition to specific therapies directed against severe hyperthyroidism, the complications of thyrotoxic crisis were treated on the intensive care unit during hospitalization. The present discussion focuses primarily on the neuromuscular complications that developed during the period of treatment for thyrotoxic crisis in these two patients.

Several mechanisms may have contributed to the severe flaccid quadriplegia observed in both patients. Thyroid hormones have multiple effects on muscle cell metabolism, with excess hormones having a catabolic effect on muscle (3). Consequently, muscle weakness and wasting are common clinical manifestations of thyrotoxicosis. Thyrotoxic myopathy is usually most evident in the proximal limb muscles, and it may involve muscles in the more distal extremities, trunk and face in severe cases (4). Although the serum thyroid hormone levels were strongly elevated, the weakness observed in the two current patients was rapidly progressive and quite severe in both the proximal and distal muscles. Accordingly, severe thyrotoxicosis itself cannot fully explain the flaccid quadriplegia observed in each case. In general, the severity of muscle weakness correlates with the duration, rather than biochemical severity, of thyrotoxicosis (3), and muscle strength normalizes once a normal metabolic state is restored, although the muscle mass takes longer to recover (4). In both of the present cases, the muscle strength did not fully recover until long after the serum thyroid hormone levels normalized. In particular, the patient in Case 1 was emaciated due to thyrotoxicosis and had lost a significant amount of muscle mass prior to admission, which may have partly contributed to the severity of muscle weakness observed during hospitalization.

Disorders that should be considered in the differential diagnosis of critically ill patients who develop flaccid generalized weakness include critical illness myopathy (CIM), critical illness polyneuropathy (CIP) or both (critical illness polynuromyopathy). CIM, a myopathy, and CIP, an axonal neuropathy, may develop during the treatment of critical illnesses (5) and are pathophysiologically complex, involving metabolic, inflammatory and bioenergetic alterations (6). In the two present patients, the muscle weakness was quite severe and symmetric, exhibiting rapid progression during the treatment of thyrotoxic crisis and multiple organ failure. In addition, both patients were mechanically ventilated under sedation prior to developing quadriplegia. Accordingly, the quadriplegia was presumably attributed primarily to CIM and/or CIP. In each case, it is generally difficult to distinguish between CIM, CIP and combined CIM/CIP using clinical and/or neurological examination findings alone. In the two current cases, neither thorough electrophysiological examinations nor a muscle biopsy were performed; therefore, it was not possible to obtain a definitive diagnosis of CIM and/or CIP.

Glucocorticoids have direct catabolic effects on skeletal muscle through their actions on intermediary metabolism by supplying amino acids for gluconeogenesis (7). Glucocorticoids generally induce a state of subacute muscle weakness over several weeks, primarily in the proximal muscles. However, treatment with higher doses of glucocorticoids may result in the rapid onset of both proximal and distal muscle weakness, as well as CIM, in critically ill patients (8). The onset of CIM usually occurs several days or more after the initiation of intravenous glucocorticoid treatment (9). The duration of hydrocortisone therapy in the present cases was not particularly long, at 23 and 15 days, respectively, and this treatment was only administered for five and 14 days, respectively, before the onset of quadriplegia. In both cases, the hydrocortisone was administered at fairly high doses under critical conditions; therefore, it may have contributed to the development of CIM as well as prolonged the recovery of muscle strength in the two patients.

Thyrotoxic crisis is often complicated by multiple organ failure, which requires treatment in an intensive care unit. The metabolic derangement associated with hyperthyroidism and hyperglycemia may increase the risk of CIM and CIP (9, 10). Moreover, the greatest risk factor for CIM is the administration of massive doses of intravenous glucocorticoids (9). The use of high doses of glucocorticoids is es-
sential for treating thyrotoxic crisis, although it often induces hyperglycemia, which requires the administration of intensive insulin therapy under extremely stressful conditions. Therefore, the onset of thyrotoxic crisis and its treatment may trigger the development of CIM and/or CIP. Only one case of CIM associated with hyperthyroidism has been previously reported (10); however, both CIM and CIP may sometimes occur among patients receiving treatment for thyrotoxic crisis in the intensive care unit.

Finally, the coexistence of rhabdomyolysis may also have contributed to the onset of prolonged and severe muscle weakness observed in Case 2. Rhabdomyolysis may induce mild to moderate weakness. Several cases of rhabdomyolysis associated with thyrotoxicosis have been reported (11, 12), and hyperthyroidism may cause rhabdomyolysis by increasing the energy consumption associated with the depletion of muscle energy stores and substrates (11). In addition, rhabdomyolysis may occur as a complication of dehydration and electrolyte imbalances (12).

In conclusion, reversible flaccid quadriplegia is a potentially serious neuromuscular condition that may occur during the treatment of thyrotoxic crisis. When managing patients with thyrotoxic crisis, the potential for neuromuscular complications associated with thyrotoxicosis itself as well as multiple organ failure and consequent treatment should be considered.

The authors state that they have no Conflict of Interest (COI).

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