Abstract

A 51-year-old woman presented with flexion contractures of the legs. Physical examination showed decreased passive movements of the bilateral hip and knee joints without muscle spasms or neurological abnormalities. Laboratory evaluation showed no response of ACTH or plasma cortisol to stimulation with CRH or insulin. Diagnosis of isolated adrenocorticotropic hormone deficiency was made. The patient was started on prednisolone 5 mg daily, and flexion contractures of the legs rapidly disappeared. Although the musculoskeletal manifestation of this patient is similar to that of stiff-person syndrome, flexion contracture of the legs associated with adrenocortical insufficiency seems to be a separate disease entity from stiff-person syndrome.

Key words: flexion contracture of legs, adrenocortical insufficiency, stiff-person syndrome

Case Report

A 51-year-old woman presented with a three-year history of flexion contractures of the legs. She complained that every time she sat on a chair for longer than ten minutes, she had difficulties with standing up. Three years prior to this visit to our hospital, she began to experience muscle stiffness in lumbar and thigh areas. Physical examination showed decreased passive movements of the bilateral hip and knee joints. No muscle spasms or neurological abnormalities were elicited. The thyroid gland was not palpable. There was no skin pigmentation.

Laboratory evaluation showed a white blood cell count of 6.0x10^9/l with differential counts of 54.3% neutrophils, 39.9% lymphocytes, 3.7% monocytes, 1.2% eosinophils and 0.9% basophils, a hemoglobin of 8.5 g/dl and mean corpuscular volume (MCV) of 65.7 fl. The serum glucose was 97 mg/dl, the sodium 140 mEq/l, the potassium 4.1 mEq/l, aspartate aminotransferase 20 IU/l, alanine aminotransferase 8 IU/l, lactate dehydrogenase 202 IU/l, creatine kinase (CK) 220 IU/l, total cholesterol 147 mg/dl. Neither rheumatoid factor nor C-reactive protein was positive. The X-ray of hip and knee joints disclosed no remarkable findings.

Iron deficiency anemia and primary hypothyroidism were suspected, and confirmed biochemically with a serum ferritin level less than 3.0 ng/ml, serum concentration of thyroid stimulating hormone 20.0 mU/l and free thyroxine 0.60 ng/dl. Neither anti-thyroid peroxidase antibody nor antithyroglobulin antibody was identified. The patient was started on ferrous 105 mg and thyroxine 50 µg daily. Two weeks later thyroxine was increased to 100 µg daily. The thyroid function as well as the hemoglobin level was returned to normal without an improvement of flexion contractures.

The basal plasma cortisol level was less than 1.0 µg/dl and failed to rise after cosyntropin test, whereas the basal adrenocorticotropic hormone (ACTH) level was less than 4.8 pg/ml. Assessment of hypothalamic and pituitary function

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Flexion Contractures of the Legs

revealed that: 1) the basal ACTH and plasma cortisol level were extremely low, and showed no response to stimulation by corticotropin releasing hormone (CRH) or insulin tolerance test. 2) thyroid stimulating hormone (TSH), prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH) and growth hormone (GH) level showed sufficient responses (Table 1). The cranial MRI showed no remarkable findings in hypothalamic and pituitary area. Serum dehydroepiandrosterone-sulfate (DHEA-S) level was less than 10 ng/ml (reference value: 60–1,230 ng/ml). Plasma aldosterone concentration and plasma renin activity level in supine position were 47 pg/ml (reference value: 45.0–105.5 pg/ml) and 0.93 ng/ml/hour (reference value: 0.2–2.7 ng/ml/hour), respectively. These results indicated the diagnosis of isolated ACTH deficiency and primary hypothyroidism.

Anti-glutamic acid decarboxylase (GAD) antibody was not detected. An electromyogram (EMG) showed combined neuropathic and myopathic changes in midlumbar paraspinal muscle and sartorius muscle. Neither clinical findings nor the electromyographic activities were compatible with stiff-person syndrome. The patient was started on prednisolone 5 mg daily, and flexion contractures of the legs rapidly disappeared in two weeks (Fig. 1).

Discussion

We presented a patient with flexion contracture of the bilateral hip and knee joints complicated by progressive, proximal leg muscle stiffness. The clinical picture of this patient resembled stiff-person syndrome (also called stiff-man syndrome). The diagnostic criteria for stiff-person syndrome were proposed by Lorish et al (2), and Helfgott (3) (Table 2). Our patient fulfilled only some of these criteria. She showed findings of a prodrome of stiffness and rigidity, slow progression of stiffness, fixed deformity of the spine, normal findings on motor and sensory nerve examinations, and normal intellect. She, however, did not have findings crucial for the diagnosis of stiff-person syndrome, including episodic spasms, continuous motor-unit activity on electromyogram and anti-glutamic acid decarboxylase antibody. In addition, she presented evidence for adrenal insufficiency and responded promptly to the physiological dose of glucocorticoid.

Increased muscle mass, muscle stiffness with muscle weakness and a low level of serum thyroxine are known as Hoffmann’s syndrome (4). Klein et al (4) reported patients with a CK elevation of ten times more than normal where the muscle abnormalities were completely resolved after

Table 1. Plasma Hormone Level

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH test* (protireline 0.5 mg)</td>
<td>TRH (µU/ml)</td>
<td>2.6</td>
<td>13.1</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>Free T4 (ng/dl)</td>
<td>1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolactin (ng/ml)</td>
<td>12.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH-RH stimulation test</td>
<td>LH (mIU/ml)</td>
<td>23.9</td>
<td>64</td>
<td>75</td>
</tr>
<tr>
<td>(gonadorelin acetate 0.1 mg)</td>
<td>FSH (mIU/ml)</td>
<td>38</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>ACTH test</td>
<td>Cortisol (µg/dl)</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>(tetracosactide acetate 0.25 mg)</td>
<td>Insulin test (insulin injection 5U)</td>
<td>GH (ng/ml)</td>
<td>1.8</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>ACTH (pg/ml)</td>
<td>&lt;5.9</td>
<td>&lt;5.9</td>
<td>&lt;5.9</td>
</tr>
<tr>
<td></td>
<td>Cortisol (µg/dl)</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose (mg/dl)</td>
<td>74</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>CRH test (corticorelin 100 µg)</td>
<td>ACTH (pg/ml)</td>
<td>&lt;5.9</td>
<td>&lt;5.9</td>
<td>&lt;5.9</td>
</tr>
<tr>
<td></td>
<td>Cortisol (µg/dl)</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

*Being treated with L-thyroxine 100 µg daily. TRH: thyrotropin-releasing hormone, TSH: thyroid stimulating hormone, LH-RH: luteinizing hormone-releasing hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, GH: growth hormone, ACTH: adrenocorticotropic hormone.

Figure 1. Clinical course.
Table 2. Proposed Diagnostic Criteria for Stiff-man Syndrome

1. Prodrome of stiffness and rigidity in axial muscles.
2. Slow progression of stiffness resulting in impairment of ambulation.
3. Fixed deformity of the spine, in general, and pronounced lordosis.
4. Presence of superimposed episodic spasms precipitated by sudden movement, noise, or emotional upset.
5. Normal findings on motor and sensory nerve examinations.
6. Continuous motor-unit activity on electromyogram abolished by intravenous diazepam or positive therapeutic response to oral diazepam.
7. Normal intellect.
8. Presence of either anti-glutamic acid decarboxylase antibodies (60% of patients) or antiamphiphysin antibodies (<5% of patients).

Adapted from Helfgott (3).

thyroxine replacement therapy. The elevation of serum CK in the present case was not surprisingly marked and recovered to normal after six weeks of thyroxine therapy. Complete relief of muscle stiffness in response to steroid replacement after failure of thyroxine therapy indicated that the muscular symptoms in our case were related to the adrenal insufficiency rather than hypothyroidism.

Musculoskeletal symptoms such as diffuse myalgia and arthralgia are infrequent clinical manifestations in patients with chronic adrenocortical insufficiency. Serum concentrations of muscle enzymes, muscle biopsy, and electromyography are usually normal. The mechanism of musculoskeletal symptoms accompanying chronic adrenocortical insufficiency is unknown. We suggest that glucocorticoids are necessary to maintain some metabolic functions of the muscle in addition to energy metabolism and immunosuppressive effects. The myalgia and arthralgia should rapidly disappear with glucocorticoid and mineralocorticoid replacement.

Among musculoskeletal symptoms of adrenal insufficiency, flexion contracture of the legs has been known as a rare manifestation (5, 6). Chroni et al reported a case of flexion contractures of the legs complicated with panhypopituitarism (7). The patient did not respond to diazepam, phenytoin, or botulinum toxin type A, which are used as standard treatments for stiff-person syndrome, but the symptom was relieved by replacement of hydrocortisone and thyroxine. George and colleagues also reported a patient with flexion contractures of the legs accompanied with pituitary deficiency of ACTH, GH, and prolactin who improved within several days on hydrocortisone (8).

The latest reference emphasized the usefulness of basal plasma ACTH concentration measurement (9). When coupled with simultaneous measurement of basal serum cortisol, the measurement of plasma ACTH can both confirm the diagnosis of adrenal insufficiency and establish its cause. Cortisol secretion is deficient in patients with primary adrenal insufficiency despite the fact that their ability to secrete ACTH is intact. Conversely, patients with secondary or tertiary adrenal insufficiency have intrinsically normal but atrophic adrenal glands that are capable of producing cortisol but fail to do so because ACTH secretion is deficient. Measurement of the basal plasma ACTH concentration can generally differentiate between these disorders. We did not perform a prolonged ACTH stimulation test to rule out primary adrenal insufficiency, since our patient had a distinctively low basal serum cortisol and plasma ACTH.

Primary adrenal insufficiency as well as other endocrine abnormalities is associated with polyglandular autoimmune (PGA) syndrome. Autoimmune thyroid disease, usually chronic autoimmune thyroiditis, type 1 diabetes mellitus, and antibodies to steroidogenic enzymes are common in this disorder. The clinical features of our patient were not consistent with those of PGA. Neither autoantibodies against thyroid gland nor anti-GAD antibody was detected. Therefore, PGA was essentially ruled out.

In conclusion, flexion contracture of the legs associated with adrenocortical insufficiency is a separate disease entity from stiff-person syndrome with a different pathophysiological basis and an effective treatment. Adrenocortical insufficiency should be considered in the differential diagnosis of flexion contractures of the legs.

References


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