Severe thyroid-associated orbitopathy in Hashimoto’s thyroiditis. Report of 2 cases

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Abstract. Thyroid-associated orbitopathy (TAO) is characterized by immune-mediated inflammation of the extraocular muscles surrounding orbital connective tissue and adipose tissue. Severe orbitopathy related to autoimmune thyroid disease often occurs in patients with Grave’s disease, but it is rare in patients with Hashimoto’s thyroiditis. The pathogenesis of TAO is unclear. Several studies have noted a strong correlation between the levels of antibodies to thyrotropin receptor antibody (TRAb) and TAO in Graves’ disease. Mild upper eyelid retraction has been reported to be common in Hashimoto’s thyroiditis patients, however severe orbitopathy is rare. We report two cases of severe TAO in patients with Hashimoto’s thyroiditis who required systemic glucocorticoid therapy and orbital irradiation to treat the TAO. The activity of the TAO was high in both patients, because their clinical activity scores (CAS) for the orbitopathy were high, and magnetic resonance imaging (MRI) showed enlargement of the extraocular muscles and an increase in T2 signal intensity and prolonged T2 relaxation time which indicate an active stage of inflammation. We tested the presence of TRAb by three different assays and were negative in both patients. Since the eye muscle damage cannot be due to TSH receptor antibodies, other pathogenetic mechanisms may be responsible for the orbitopathy in patients with Hashimoto’s thyroiditis.

Key words: Hashimoto’s thyroiditis, Thyroid-associated orbitopathy, Thyrotropin receptor antibody

THYROID-ASSOCIATED orbitopathy (TAO) is characterized by immune-mediated inflammation of the extraocular muscles surrounding orbital connective tissue and adipose tissue. TAO generally occurs in patients with hyperthyroidism due to Graves’ disease, and it sometimes occurs in euthyroid and hypothyroid patients. Most euthyroid and hypothyroid patients with TAO are thyrotropin receptor antibody (TRAb) -positive, and they are diagnosed as having euthyroid Graves’ disease or hypothyroid Graves’ disease. Although it is widely accepted that TAO is an autoimmune disorder, its pathogenesis is unclear. Several studies have noted a strong correlation between antibodies to thyrotropin receptor and TAO in Graves’ disease [1-6], and serum TRAb levels have been found to correlate positively with clinical features of orbitopathy [7]. The TRAb hypothesis cannot be used to explain TAO in Hashimoto’s thyroiditis, because Hashimoto’s thyroiditis patients usually test negative for TRAb. Mild upper eyelid retraction has been reported to be common in Hashimoto’s thyroiditis patients [8]. Severe orbitopathy is rare in Hashimoto’s thyroiditis, and only a few cases have ever been reported [9-11]. We report two cases of severe TAO in Hashimoto’s thyroiditis.

Laboratory Methods

TSH and free thyroxine (fT4) levels were measured by electrochemiluminescence immunoassays (ECLusys TSH and ECLusys FT4, respectively; Roche Diagnostics GmbH, Mannheim, Germany). The manufacturer’s reference limits were 0.2-4.5 mU/L and 10.3 – 20.6 pmol/L, respectively. TSH receptor antibody (TRAb: thyrotropin binding inhibitory immunoglobulin) levels were determined with a commercial
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radioimmunoassay kit (RSR, Cardiff, UK; TRAb-CT) and expressed as percentage (%) inhibition of binding according to the manufacturer’s instructions (normal range <10%). We also determined TRAb by a two-step radioreceptor assay (DYN0 test TRAb Human Kit “YAMASA”; Yamasa Corp., Tokyo, Japan: normal range <1.0 IU/L; TRAb-Dyno). Thyroid-stimulating antibody (TSAb) was measured with a commercial bioassay radioimmunoassay kit (Yamasa Corp., Tokyo, Japan) and expressed as a percentage of cAMP production generated in porcine thyroid cells that contained test pooled immunoglobulin (normal range, <180%). TSH-stimulation blocking antibody (TSBAb) activity was assayed by measuring inhibition of TSH-induced cAMP production, with values above 45% indicating the presence of TSBAb activity. Anti-thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) were determined by solid-phase RIAs (Cosmic Corp., Tokyo, Japan), and the normal range of both is below 0.3 U/mL.

Case Reports

Case 1

A 64-year-old woman consulted an ophthalmologist with a chief complaint of diplopia, and an ophthalmological examination showed a mild supraduction deficiency. Laboratory examination results indicated hypothyroidism; the TSH level was 37.8 mU/L. The TPOAb level was >60 U/mL, and TRAb-CT was <0.1%. The patient had never smoked. She was diagnosed with Hashimoto’s thyroiditis and treated with levothyroxine 50 µg daily for the hypothyroidism and with oral prednisone, 30 mg daily tapered by 10 mg per month, for the orbitopathy. Despite this treatment, the diplopia became exacerbated 7 months later, and magnetic resonance imaging (MRI) showed enlargement of the left medial rectus muscle and left inferior rectus muscle. The active form of orbitopathy was diagnosed, and methylprednisolone pulse therapy was administered, but when her diplopia failed to improve, she was referred to our hospital for further examination and treatment. When first examined at our hospital the patient was being treated with levothyroxine 50 µg daily, and her TSH level was 3.81 mU/L. Her thyroid hormone levels were within the reference values. TRAb testing was negative; the results were 7.5% by TRAb-CT and below 1.0 IU/L by TRAb-Dyno. A TSAb test was also negative (126%). The TgAb level was 7.2 U/mL, and the TPOAb level was 50 U/mL. Ultrasonography showed a thyroid gland with heterogeneously decreased echogenicity and no nodules. The laboratory data are shown in Table 1. The degree of exophthalmoses measured with the Hertel exophthalmometer was 15 mm in both eyes. The clinical activity score (CAS) for the orbitopathy in this patient was

Table 1. Clinical course and laboratory data in Case 1.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>fT4 (pmol/L)</th>
<th>TSH (mU/L)</th>
<th>TRAb-CT (%)</th>
<th>TRAb-Dyno (IU/L)</th>
<th>TSAb (%)</th>
<th>TSBAb (%)</th>
<th>TgAb (U/mL)</th>
<th>TPOAb (U/mL)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year before</td>
<td>37.8</td>
<td>&lt;0.1</td>
<td>126</td>
<td>&gt;60</td>
<td>LT4 50 µg following methylprednisolone pulse therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit</td>
<td>18.0</td>
<td>3.81</td>
<td>7.5</td>
<td>&lt;1.0</td>
<td>7.2</td>
<td>&gt;50</td>
<td>LT4 50 µg + orbital irradiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 months</td>
<td>12.6</td>
<td>62.45</td>
<td>151</td>
<td>LT4 100 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 months</td>
<td>23.8</td>
<td>0.32</td>
<td>4.6</td>
<td>LT4 100 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 months</td>
<td>26.3</td>
<td>0.06</td>
<td>20</td>
<td>LT4 75 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 months</td>
<td>18.3</td>
<td>0.69</td>
<td>83</td>
<td>LT4 75 µg + orbital decompression surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 months</td>
<td>17.5</td>
<td>1.93</td>
<td>37</td>
<td>LT4 75 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 years</td>
<td>18.0</td>
<td>0.79</td>
<td></td>
<td>LT4 75 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Levothyroxine was administered to treat the patient's hypothyroidism, and methylprednisolone pulse therapy, orbital irradiation, and orbital decompression surgery were performed to treat the orbitopathy. TRAb and TSAb tests have remained negative during the 6-year follow-up period. fT4: free thyroxine (normal range: 10.3–20.6 pmol/L), TSH: thyrotropin (normal range: 0.2–4.5 mU/L), TRAb-CT: TSH receptor antibody (normal range: <10%), TRAb-dyno: TSH receptor antibody (normal range: <1.0 IU/L), TSAb: Thyroid-stimulating antibody (normal range: <180%), TSBAb: TSH stimulation blocking antibody (normal range: <45%), TgAb thyroglobulin antibody (normal range: <0.3 U/mL), TPOAb: Anti-thyroid peroxidase antibody (normal range: <0.3 U/mL)

LT4: levothyroxine, PSL: prednisolone
Orbitopathy in Hashimoto’s thyroiditis

Case 1

A 60-year-old woman had bilateral blepharoptosis and diplopia for several months. Subsequently she consulted a neurologist and an ophthalmologist. MRI of the eyes revealed bilateral enlargement of the medial rectus muscle and inferior rectus muscle and an increase in T2 signal intensity and prolonged T2 relaxation time (Fig. 1). Exophthalmos measured by Hertel exophthalmometry was 17 mm in the right eye and 16 mm in the left eye. The laboratory data indicated subclinical hypothyroidism; the TSH level was 8.16 mU/L, and the free thyroxine (fT4) level 15.2 pmol/L. The TPOAb level was >50 U/mL, TgAb 1160 U/mL, TRAb below 0.1%, TSAb was 113%. The patient had never smoked. She was treated with levothyroxine 75 µg daily. There was slight improvement in the diplopia. Orbital decompression surgery was then performed, and the diplopia finally resolved. Her thyroid function has remained stable during 6 years of treatment with levothyroxine 75 µg daily.

Fig. 1 Magnetic resonance imaging (MRI) of the eyes in Case 1 showed enlargement of the left medial rectus muscle and left inferior rectus muscle (yellow arrows).

Case 2

A 44-year-old woman suffered from bilateral blepharoptosis and diplopia for several months. Subsequently she consulted a neurologist and an ophthalmologist. MRI of the eyes revealed bilateral enlargement of the medial rectus muscle and inferior rectus muscle and an increase in T2 signal intensity and prolonged T2 relaxation time (Fig. 2). Exophthalmos measured by Hertel exophthalmometry was 17 mm in the right eye and 16 mm in the left eye. The laboratory data indicated subclinical hypothyroidism; the TSH level was 8.16 mU/L, and the free thyroxine (fT4) level 15.2 pmol/L. The TPOAb level was >50 U/mL, TgAb 1160 U/mL, TRAb below 0.1%, TSAb was 113%. The patient had never smoked. She was treated with levothyroxine 75 µg daily. There was slight improvement in the diplopia. Orbital decompression surgery was then performed, and the diplopia finally resolved. Her thyroid function has remained stable during 6 years of treatment with levothyroxine 75 µg daily.

Fig. 2 MRI of the eyes in Case 2 revealed bilateral enlargement of the medial rectus muscle and inferior rectus muscle (yellow arrows).
orbital myositis are orbital pain exacerbated by eye movement and a rapid response to systemic corticosteroid therapy, but neither of our patients complained of orbital pain, thereby ruling out idiopathic orbital myositis. IgG4-related disease is a recently proposed clinical entity that is characterized by several unique clinical findings. Ocular adnexal IgG4-related disease is often manifested by enlargement of lacrimal and salivary glands, but the extraocular muscles are usually not involved [17, 18]. The main clinical signs of TAO include exophthalmos, eyelid retraction and lag, diplopia and optic neuropathy. In the early stages of TAO the inflamed and enlarged eye muscle does not stretch normally, leading to double vision as a consequence [19]. In the previous study which evaluated the extraocular muscle enlargement in TAO in Graves’ disease, the most frequently affected muscle was the inferior rectus muscle, followed by the medial rectus muscle [7, 20]. In our cases, left medial rectus muscle and left inferior rectus muscle were enlarged in case 1, bilateral medial rectus muscle and inferior rectus muscle were enlarged in case 2. The typical MRI findings, clinical course, and the presence of antibodies to thyroid antigens in our two patients led to the diagnosis of TAO. The activity of the TAO was high in both patients, because a CAS of 3 or more indicates active orbitopathy [21], and increased T2 signal intensity and a prolonged T2 relaxation time indicate an active stage of inflammation [22].

Severe orbitopathy is rare in patients with Hashimoto’s thyroiditis, and only few such cases have been reported [9-11]. In one of the cases the patient was reported to be TRAb-positive, and hypothyroidism 75 µg daily for subclinical hypothyroidism, and referred to our hospital. Examination yielded a CAS of 4: one point each for a painful oppressive feeling behind the globe, redness of the eyelids, swelling of the eyelids, and increased proptosis. She was treated with orbital irradiation (15 Gy), and the diplopia improved slightly. The patient was also treated with oral prednisone 15 mg daily, and the dose was tapered in 5 mg decrements depending on the symptoms. The diplopia gradually improved after the start of treatment. TRAb and TSAb test results have remained negative during the 6-year follow-up period (Table 2). The symptoms and thyroid function have remained stable during the 6 years of treatment with levothyroxine 75 µg daily.

**Table 2** Clinical course and laboratory data in Case 2.

<table>
<thead>
<tr>
<th>Case 2</th>
<th>fT4 (pmol/L)</th>
<th>TSH (mU/L)</th>
<th>TRAb-CT (%)</th>
<th>TRAb-Dyno (IU/L)</th>
<th>TSAb (%)</th>
<th>TgAb (U/mL)</th>
<th>TPOAb (U/mL)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 months before</td>
<td>15.2</td>
<td>8.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LT4 75 µg</td>
</tr>
<tr>
<td>4 months before</td>
<td>14.7</td>
<td>5.95</td>
<td>&lt;0.1</td>
<td></td>
<td>113</td>
<td>1160</td>
<td></td>
<td>LT4 75 µg and orbital irradiation + PSL 15 mg tapered gradually</td>
</tr>
<tr>
<td>First visit</td>
<td>11.2</td>
<td>6.62</td>
<td>8</td>
<td>&lt;1.0</td>
<td></td>
<td></td>
<td></td>
<td>LT4 75 µg and PSL 5 mg</td>
</tr>
<tr>
<td>1 month</td>
<td>17.0</td>
<td>2.62</td>
<td></td>
<td></td>
<td>128</td>
<td></td>
<td></td>
<td>LT4 75 µg and PSL 5 mg</td>
</tr>
<tr>
<td>2 months</td>
<td>16.7</td>
<td>1.31</td>
<td></td>
<td></td>
<td>138</td>
<td></td>
<td></td>
<td>LT4 75 µg and PSL 5 mg</td>
</tr>
<tr>
<td>5 months</td>
<td>16.0</td>
<td>2.36</td>
<td></td>
<td>93</td>
<td>61.1</td>
<td>&gt;50</td>
<td></td>
<td>LT4 75 µg and PSL 5 mg</td>
</tr>
<tr>
<td>8 months</td>
<td>21.5</td>
<td>0.34</td>
<td>4.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LT4 75 µg</td>
</tr>
<tr>
<td>6 years</td>
<td>15.2</td>
<td>4.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LT4 75 µg</td>
</tr>
</tbody>
</table>

Levothyroxine was administered to treat subclinical hypothyroidism, and orbital irradiation and oral prednisone were used to treat the orbitopathy. TRAb and TSAb tests have remained negative throughout the 6-year follow-up period, and the patient’s symptoms and thyroid function have been stable during the follow-up period.

Discussion

TAO usually occurs in Graves’s disease with hyperthyroidism, and sometimes in euthyroid and hypothyroid patients. Since most euthyroid and hypothyroid patients with orbitopathy are TRAb-positive, they are diagnosed as having euthyroid Graves’ disease or hypothyroid Graves’ disease. When euthyroid and hypothyroid patients with orbitopathy are TRAb-negative, other diseases need to be considered in the differential diagnosis, including cavernous carotid fistula, sphenoid meningioma, other orbital tumors, such as lymphoma, idiopathic orbital myositis [12], and IgG4-related disease [13-15]. MRI of the brain showed no signs of a tumor occupying the orbital cavity or of a cavernous carotid fistula in either Case 1 or Case 2. Neither patient had any clinical manifestations of lymphoma [16]. The main clinical features of idiopathic orbital myositis are orbital pain exacerbated by eye movement and a rapid response to systemic corticosteroid therapy, but neither of our patients complained of orbital pain, thereby ruling out idiopathic orbital myositis. IgG4-related disease is a recently proposed clinical entity that is characterized by several unique clinical findings. Ocular adnexal IgG4-related disease is often manifested by enlargement of lacrimal and salivary glands, but the extraocular muscles are usually not involved [17, 18]. The main clinical signs of TAO include exophthalmos, eyelid retraction and lag, diplopia and optic neuropathy. In the early stages of TAO the inflamed and enlarged eye muscle does not stretch normally, leading to double vision as a consequence [19]. In the previous study which evaluated the extraocular muscle enlargement in TAO in Graves’ disease, the most frequently affected muscle was the inferior rectus muscle, followed by the medial rectus muscle [7, 20]. In our cases, left medial rectus muscle and left inferior rectus muscle were enlarged in case 1, bilateral medial rectus muscle and inferior rectus muscle were enlarged in case 2. The typical MRI findings, clinical course, and the presence of antibodies to thyroid antigens in our two patients led to the diagnosis of TAO. The activity of the TAO was high in both patients, because a CAS of 3 or more indicates active orbitopathy [21], and increased T2 signal intensity and a prolonged T2 relaxation time indicate an active stage of inflammation [22].

Severe orbitopathy is rare in patients with Hashimoto’s thyroiditis, and only few such cases have been reported [9-11]. In one of the cases the patient was reported to be TRAb-positive, and hypothyroid
Graves’ disease was suspected [9]. Since the other two case reports did not mention the presence of TRAb [10, 11], hypothyroid or euthyroid Graves’ disease could not be excluded.

The pathogenesis of TAO and the mechanism of the link to thyroid autoimmunity are poorly understood. Several antigens have been identified as possible autoantibody targets, including TRAb [23, 24], the skeletal muscle calcium binding protein calsequestrin, and the fibroblast cell membrane protein collagen XIII [25-28]. There is accumulating evidence that the TSH receptor is present in the orbit and expressed on orbital fibroblasts. These findings support the hypothesis that TRAb is not only the cause of Graves’ disease, but is also responsible for TAO. Hashimoto’s thyroiditis is not usually associated with overt orbitopathy, however, Tjiang et al. reported that mild eye signs were present in 34% of their patients [8], and they predominantly consisted of upper eyelid retraction. Since patients with Hashimoto’s thyroiditis test negative for TRAb, the TRAb hypothesis cannot be used to explain the etiology of eye signs in Hashimoto’s thyroiditis. An alternative explanation for the orbitopathy in patients with Hashimoto’s thyroiditis is specific production of antibody against an eye muscle antigen, such as calsequestrin, flavoprotein, or G2s [29]. We did not test either of our two patients for such antibodies, and further investigation is needed. We have reported two cases of severe TAO in which testing for the presence of TRAb by three different assays was negative. Since the eye muscle damage cannot be due to TSH receptor antibodies, other pathogenetic mechanisms may be responsible for the orbitopathy in patients with Hashimoto’s thyroiditis.

References


