A case of Graves’ disease presenting with internal ophthalmoplegia during methylmercaptoimidazole treatment

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Abstract. A 28-year-old Japanese woman positive for TSH receptor antibody and anti-nuclear antibody complained of difficulty seeing nearby objects, severe throbbing retro-orbital pain, diplopia, blepharoptosis and upward gaze palsy when she became hypothyroid during treatment with 30 mg methylmercaptoimidazole for Graves’ hyperthyroidism. Brain magnetic resonance imaging revealed slightly swollen bilateral inferior rectus muscles, suggesting the external ophthalmoplegia due to the muscle pathology commonly encountered in Graves’ disease. The retro-orbital pain was associated with marked accommodation failure and the pupillary abnormalities. The left and/or right eye showed intermittent, asymmetric and fluctuating mydriasis, being unresponsive to ordinary light but slowly responsive to strong sunlight and slowly responsive in a dark room. During the 5-year period, mydriasis was observed 9 times on both sides, 11 times only on the right side and 4 times only on the left side. Internal ophthalmoplegia with tonic pupils and accommodation failure affecting both the pupillary sphincter muscle and ciliary muscle due to damage to the parasympathetic outflow to these muscles was suggested. Autoimmune mechanism and/or the mechanism underlying channelopathy affecting the ciliary ganglion or short ciliary nerves might be responsible for this fluctuating complication. This very rare panophthalmopathy affecting both external and internal muscles occurred when the patient was suffering from iatrogenic hypothyroidism during the 30 mg methylmercaptoimidazole treatment for Graves’ disease.

Key words: Hyperthyroidism, Graves’ disease, Graves’ ophthalmopathy, Internal ophthalmoplegia, Tonic pupil

IT IS WELL KNOWN that Graves’ disease is associated with ophthalmopathy, affecting extraocular muscles and retrobulbar adipose tissues [1]. In contrast, disorders of the pupillary function or accommodation [2] are extremely rare and not included in the NOSPECS classification [3] or the Clinical Activity Score (CAS) [4] of Graves’ ophthalmopathy. Pupillary disorders in Graves’ hyperthyroidism, if present, are considered an afferent defect due to dysthyroid optic neuropathy [1], although Adie’s tonic pupil was reported in hyperthyroidism [5].

We herein report a case of Graves’ disease presenting with fluctuating internal ophthalmoplegia in addition to external ophthalmoplegia during methylmercaptoimidazole (MMI) treatment. To our knowledge, this is the first such case report.

Case Report

A 28-year-old Japanese woman noticed tachycardia and weight loss in May. Her serum TSH level was <0.01 μU/mL (reference value 0.42–3.81 μU/mL), free T4 5.2 ng/dL (0.8–1.7 ng/dL), anti-thyroglobulin antibody 100 (<100), antithyroid microsomal antibody 800 (<100) and TSH Receptor antibody (TRAb) 48% (<15%). With a diagnosis of Graves’ hyperthyroidism, she was treated with MMI 30 mg daily. The results of a visual acuity test before treatment were very good: 1.5 for both eyes. She soon became hypothyroid (free T4 0.4 ng/dL), gaining 5 kg of weight and developing non-pitting edema on the legs. She then developed throbbing retro-orbital pain mainly in the right eye associated with nausea and diplopia, requiring more than 200 mg diclofenac...
Na every day. She felt that the light was extremely bright and dazzling. She also found it difficult to see nearby objects, read books or watch television. Looking out the window of a moving bus was especially intolerable. She was referred to our hospital and admitted in October, when impairment of convergence and upward gaze was found. She was a non-smoker. Her family history revealed no other members with thyroid abnormality or migraine.

On admission, the patient was 155 cm tall and weighed 45 kg. Her pulse rate was 72/min, regular, and her blood pressure was 104/30 mmHg. Small struma of approximately 25 g was palpable. There were no abnormalities in the ocular fundi. Blepharoptosis was noted bilaterally, and was not improved by an edrophonium (Tensilon) test. Her pupils were round and isocoric, but the light reflex was sluggish on the right. Convergence was impossible. The right eye was slightly deviated upward (Fig. 1). The eye movement was normal except for the limited upward gaze. The upward oculocephalic reflex was absent. A red-green test revealed bilateral upward gaze palsy. Hertel ophthalmometry revealed 17/17 mm. The corneal reflex was absent on both sides. Visual acuity was Rt 0.15 (0.2x–1.0) and Lt 0.2 (0.4x–1.0). The near point was 20 cm for both eyes, and the far point was 30 cm for the left eye and 25 for the right eye. Flicker values were 43, 41and 42 Hz (Rt) and 37, 37 and 37 Hz (Lt) (Reference value 35–50 Hz). The intraocular pressure was normal. A neurological examination of the extremities and trunk revealed no abnormalities. Tendon reflexes were all normal except for a sluggish achiles tendon reflex. There were no abnormalities, such as orthostatic hypotension or an abnormal heart rate, suggesting autonomic nerve dysfunction.

Blood tests revealed no abnormalities except for positive anti-nuclear factor (ANF) (homogeneous and speckled type). Acetylcholine receptor antibody was negative. Brain magnetic resonance imaging (MRI)
suggested slightly swollen bilateral inferior rectus muscles. There were no abnormalities on an electroencephalogram (EEG).

She became euthyroid on 5 mg MMI every other day (Fig. 1). Methylprednisolone pulse therapy (500 mg/day for 3 days) was given, but it was not effective for the ocular symptoms or for the retro-orbital pain. The retro-orbital pain was so severe that she required repeated retrobulbar steroid injection, which ameliorated the pain for about two to four weeks. Stellate ganglion block was not effective.

When she was evaluated in January the next year, anisocoria was apparent. Subsequently the side of mydriasis and retro-orbital pain varied depending on the time of the examination (Figs. 1 and 2). Usually, the pupil of the painful eye was dilated and almost unresponsive to penlight (Fig. 2: C–F). However, the dilated pupil responded slowly to strong sunlight and dilated again slowly when placed in a dark room (Fig. 2: E). When the pupil was smaller than 5mm, a light reflex was observed, although sluggish. She felt more pain with her eyes closed than open.

The patient became hyperthyroid again in May at 33 years old and was treated with an increased MMI dosage (Fig. 1). Anisocoria and retro-orbital pain occurred again in July (Fig. 1). The retro-orbital pain was less severe when she took a β-blocker (metoprolol) for tachycardia. She was then well controlled with a maintenance MMI dosage, and the pupils became isocoric, reacting normally to penlight. The retro-orbital pain gradually subsided when she was 35 years old and both TBII and ANF became negative. Although upward gaze palsy, occasional diplopia and accommodation difficulty remained, she had no more episodes of mydriasis or retro-orbital pain until she became 60 years old.

**Discussion**

The present case of Graves’ disease is unique in presenting with both external and internal ophthalmoplegia during MMI treatment. Based on MRI findings suggesting swollen extraocular muscles and the loss of the upward oculocephalic reflex, the external ophthalmoplegia is considered to have been due to the muscle pathology commonly encountered in Graves’ disease. In contrast, the pupillary abnormalities, characterized by an intermittent and fluctuating time course as shown in Figs. 1 and 2, were quite unusual for Graves’ disease.

Whereas increased anisocoria in darkness is induced by the inhibition of the sympathetic pathway, increased anisocoria in light is due to damage to the parasympathetic outflow to the iris sphincter muscle, classified into 1) oculomotor nerve paresis and 2) tonic pupil syndrome (pupillotonia) [2].

Pupillotonia is characterized by marked mydriasis in which the light reflex is extremely slow, and continuous exposure to the light stimulus shrinks the pupil extremely slowly. If the patient is then placed in a very dark room immediately afterwards, the pupil dilates again very slowly. Under this condition, both the pupillary sphincter and dilator muscles are considered to be in a tonic state, so it contracts as well as relaxes with extremely slow speed [6]. Pupillotonia is classified into 1) local type such as inflammation or infection, 2) neuropathic type as part of a generalized peripheral or autonomic neuropathy (e.g. syphilis or diabetes mellitus) and 3) Adie’s syndrome.

| A | Dec | Right eye | Left eye | B | Jan | Right eye | Left eye |
|---|-----|-----------|----------|---|-----|-----------|----------|
| 28 years old | LR (+) | LR (+) | | 29 years old | LR (+) | LR (+) |
| C | Jan | LR (−) | LR (+) | | | | |
| 30 years old | | | | | | | |
| D | Oct | LR (−) | LR (−) | | | | |
| 30 years old | | | | | | | |
| E | Oct | LR (+) | LR (−) | | | | |
| 31 years old | Sunlight | | |
| F | July | LR (−) | LR (+) | | | | |
| 33 years old | Darkroom | | |

Fig. 2  Chronological changes in pupil size in the present patient. At first, the pupils were isocoric, measuring about 2–3 mm, but the light reflex to ordinary penlight (LR) was sluggish on the right (A). One month later, mydriasis became apparent bilaterally, although it was asymmetric (B). When the pupil was larger than 6–7 mm, the retro-orbital pain was especially severe, and a light reflex was not observed (C, D, E, F). However, the pupil became slowly miotic on outdoor sunlight exposure and slowly mydriatic in a dark room (E).
found in otherwise healthy persons with no evidence of local orbital disease or generalized nervous system dysfunction [2].

Another feature of the present case was the patient’s inability to see near or far (accommodation failure), implying a disturbance of contraction as well as relaxation of the ciliary muscles, which suggests tonic ciliary muscle. Therefore, the present patient was suffering from internal ophthalmoplegia affecting both the pupillary sphincter and ciliary muscle. In our patient, blurred vision continued even after the improvement of tonic pupil. Compared with the pupillary control system with its antagonizing pupillary dilator and pupillary sphincter, the lens was controlled with only ciliary muscles (Fig. 3), suggesting that lens control is more vulnerable than pupil control, as experienced in patients with amblyopia. The lack of a corneal reflex was an interesting finding. A decrease in corneal sensation was reported in 10 of 11 patients with unilateral Adie’s syndrome [2].

Regarding the pathogenesis of the symptoms in the present patient suffering from Graves’ hyperthyroidism with ophthalmopathy, given the association of severe retro-orbital pain and the effectiveness of retrobulbar steroid injection, it is reasonable to speculate the involvement of fluctuating inflammatory or ischemic changes in the retrobulbar tissue affecting the ciliary ganglion or short ciliary nerves (Fig. 3). However, it is difficult to specify the character or lesions responsible for these repeated and bilateral symptoms and signs (Figs. 1 and 2). Positive ANF findings and the association with Graves’ disease suggested the involvement of some autoimmune mechanism [2, 7-9]. Given the fluctuating episodes of pupillotonia, the mechanism underlying channelopathy might also be involved in the present case [10, 11].

Of note, in the present case, external and internal ophthalmoplegia manifested during the episode of iatrogenic hypothyroidism induced by the administration of a large amount of MMI (Fig. 1), which is well known to exacerbate ophthalmopathy in Graves’ hyperthyroidism [12]. Positive TRAb and/or elevated serum TSH might stimulate the TSH receptor in the orbital preadipocyte fibroblast to exacerbate pathological lesions in the orbit [13]. The incidence of severe Graves’ ophthalmopathy was reduced after the introduction of low-dose MMI treatment in our clinic [14].

Muscle is one of the most sensitive organs to thyroid hormone, as shown by brisk and sluggish Achilles tendon reflexes being frequently found in hyper- and hypothyroidism, respectively. Likewise, the extraocular and intraocular muscles may also be influenced by thyroid hormone. Among 4,300 patients with Graves’ disease treated in our clinic over the past 50 years on medical record, the incidence of apparent internal ophthalmoplegia has been extremely low (1 case; 0.02%) compared with that of external ophthalmopathy (353; 8.2%) or periodic paralysis (83; 1.9%) (unpublished data).

**Ethical Standard**

This article does not contain any studies with human or animal subjects performed by any of the authors. The identity of the patient has been protected. The patient provided written consent for this manuscript.
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Disclosure Summary

None of the authors have any potential conflicts of interest associated with this research.

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