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Case Report

Unilateral Oculomotor Nerve Palsy Associated With Primary Hypothyroidism: Two Case Reports

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Abstract

We report two cases of unilateral oculomotor nerve palsy associated with primary hypothyroidism, both of which were admitted with monocular diplopia and ptosis as the first symptoms. On examination, there were no neurological abnormalities other than the signs of oculomotor nerve palsy. Blood biochemistry revealed a severe decrease in thyroid function with an elevation of A-TG. Cranial MRI and angiography showed no abnormalities. Thyroid hormone replacement therapy resulted in significant improvement in symptoms without meaningful changes in A-TG. Ongoing treatment found continued relief of ocular muscle palsy symptoms if thyroid function was maintained at normal levels. Our report suggests that the pathogenic mechanism may be related to the dysfunction of thyroid hormones in maintaining cellular function and enhancing β-adrenergic receptors in the eyes. In addition, this report recommends as well that clinicians should be aware that hypothyroidism may be an independent etiology of oculomotor nerve palsy.

Keywords: Hypothyroidism, Thyroid hormone, Oculomotor nerve palsy, Ptosis, Double vision, Levothyroxine

Introduction

Oculomotor nerve palsy can result from a variety of causes, including microvascular dysfunction, aneurysm compression, stroke, trauma, tumor compression, neurosurgery, and other causes, however, due to primary hypothyroidism has rarely been reported [1, 2, 3, 20].

Thyroid hormone (TH) is essential for the function and regulation of cellular metabolism in almost all mammalian cells. Clinical manifestations of hypothyroidism extend from life hostile to no signs or symptoms. The most common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin, but clinical presentation can differ with age and sex among other factors. Although ocular symptoms are additionally appeared in many patients, expressing as periorbital puffiness [1, 3, 8, 11, 12, 14, 20, 21]. To our knowledge, only a few reports have been associated with "idiopathic" oculomotor nerve palsy [6, 7]. Here we reported two cases of unilateral cranial nerve palsy due to hypothyroidism and summarized the literature on this type of disease.

Cases Presentation

Case 1

A 58-year-old woman presented to the hospital with diplopia for 2 months and a droopy right upper eyelid for 1 month. She also complained of excessive drowsiness. In the last three years, she had surgery for carpal tunnel syndrome on both sides and was noticed to have hypothyroidism and levothyroxine replacement therapy was given for 5 months, when the workup for thyroid function return to normal, she stopped it on her own. Three months prior to

admission the patient had double vision and right eyelid dropping, meanwhile, she admitted weight gain and generalized swelling. The patient denied a history of hypertension and diabetes mellitus.

Clinical examination revealed right upper lid ptosis and the right eyeball was in a "down & out" state (Figure 1: A). Restricted inward and upward movement of the right eye was seen (Figure 1: B-D). Bilateral pupils round with right pupil 3.5 mm, left pupil 2.5 mm; right pupil direct and indirect light reflexes were blunted, while the left one was sensitive. Other cranial nerve examinations showed no abnormalities. No other neurological abnormalities were seen including muscle strength and tone.

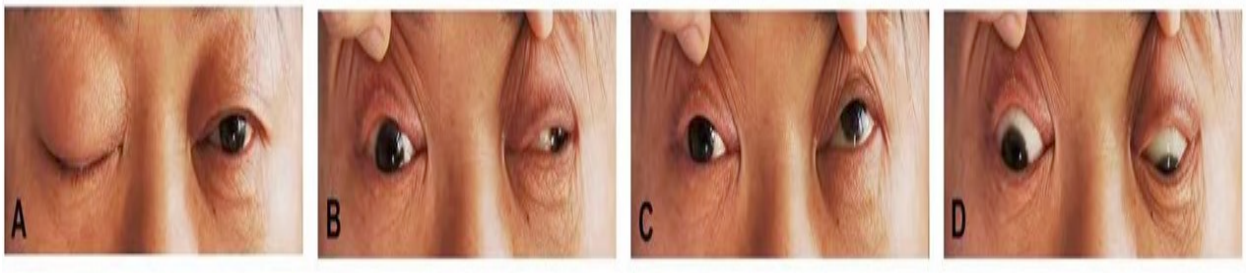

Figure 1: Showing the oculomotor nerve palsy in the right eye in Case 1. **(A)** Ptosis of the upper eyelid of the right eye. **(B-D)** Impaired inward and upward movement of the right eyeball.

Basic laboratory tests consisted of CBC, blood chemistry, coagulation screening, inflammatory markers, urinalysis, and CSF. Thyroid function and antibody tests indicated a significant decrease in free triiodothyronine (FT3) and free thyroxine (FT4) and significant increase in Thyroid stimulating hormone (TSH) (Table 1). Antithyroglobulin (A-TG) showed severe elevation (Table 1). While Anti-thyroid peroxidase (A-TPO) was mildly elevated, and moderate increase in Creatine kinase (CK) (701 U/L) was found. However, the thyrotropin receptor antibody (TRAb) values were in the normal range (Table 1). In addition, Glycosylated hemoglobin, and immune-related antibodies such as systemic lupus erythematosus, as well as tumor markers were in normal range. Lumbar puncture reveals significantly elevated protein (1.237 g/L) in the cerebrospinal fluid (CSF), while the cell count and biochemical parameters were normal.

The thyroid ultrasound showed a small thyroid gland with heterogeneous echogenicity, which was considered hypothyroidism. Head MRI showed no significant abnormalities, especially no abnormalities seen in the cavernous sinus region. No intracranial aneurysm was found on head CTA.

The final clinical diagnosis was unilateral oculomotor nerve palsy associated with primary hypothyroidism.

The treatment strategy was developed with oral levothyroxine 50 μg/day, increasing to 100 μg/day one week later. After 12 days of thyroxine treatment, the patient experienced some improvement in her symptoms. Then, Methylprednisolone 240mg with an intravenous was added once daily and was discontinued 5 days later. Right eyelid ptosis significantly improved, no diplopia found, and right eye movements became normal in all direction (Figure 2: E-H). Thyroid function tests after 30 days of treatment demonstrated FT3, FT4 and TSH in the normal range. However, the A-TG remained at 1443 IU/ml (Table 1).

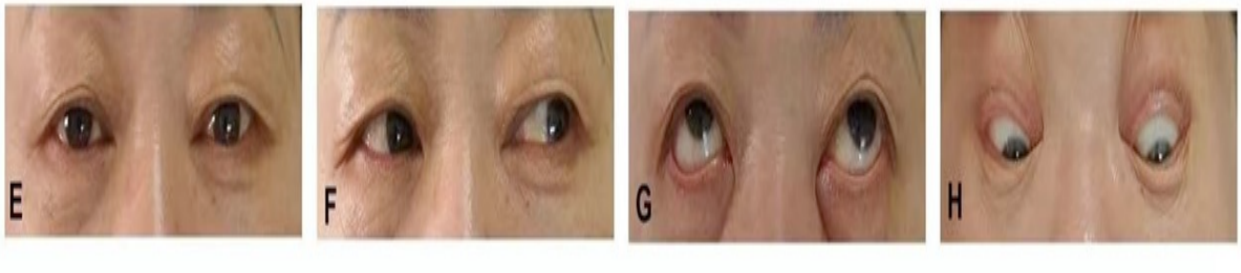

Figure 2: Showing Complete disappearance of oculomotor nerve palsy as seen on the seventh day of treatment in case 1 **(E-H)**.

Case 2

A 67-year-old female admitted to the hospital with double vision and left upper eyelid drooping for 1 week. One week ago, she developed double vision and gradual onset of left upper eyelid drooping unaccompanied by an aggravation toward the end of the day or with repetitive use. The patient denied any difficulties in speaking, chewing, or swallowing. The patient had no limb numbness or weakness, and she had no fever. She denied having a history of hypertension, diabetes, and migraines.

Physical examination showed mental status in normal range, fluent speech. Ptosis of the left eyelid was seen. Visual acuity was normal; bilateral pupils of equal size and roundness (2.5 mm). The pupillary light reflex revealed the left pupil were absent for both direct and indirect light reflexes, while the accommodation pupillary reflex appeared normal. Examination revealed that the left eyeball could not move inward and upward unaccompanied by painfulness. No abnormalities seen for the rest of the neurological examination.

Thyroid function test appeared a significant increase of TSH and decrease in FT3 and FT4 levels. While thyroid antibody profile showed A-TOP and TRAb in normal range, yet severe A-TG elevation was seen (Table 1). It is worth mentioning that after 30 days of treatment, thyroid function had normalized and the symptoms of oculomotor nerve palsy had completely disappeared, but A-TG was still above 4000 IU/ml (Table 1).

No significant abnormalities were found on head MRI and CTA. No thymoma or thymic hyperplasia detected on chest CT. Ultrasound revealed a small thyroid gland (4.8 ml) with an inhomogeneous pattern but without signs of focal lesions.

The clinical diagnosis was primary hypothyroidism-associated oculomotor nerve palsy.

Since no effect was seen, oral prednisolone 50mg/day was stopped after three days. And levothyroxine was started at 50 μg/day and gradually increased to 100 μg/day. One week later, the patient dramatically improved with complete recovery of ptosis. After 30 days of treatment, the patient's ocular symptoms completely disappeared and blood tests confirmed normal thyroid function, however, A-TG remained >4000 IU/ml (Table 1).

Lab parameter	Case 1(Value)		Case 2(Value)		Reference
	Day1	Day30	Day1	Day30	
FT3 (pg/ml)	<0.26	3.64	<0.26	3.48	2.0-4.4
FT4 (ng/dl)	<0.04	1.61	<0.04	1.61	0.93-1.7
TSH (μIU/mL)	>100	0.94	>100	5.65	0.27-4.2
A-TG (IU/ml)	1870	1443	>4000	>4000	0-115
A-TPO (IU/ml)	51.45	29.59	27.15	23.94	0-34
TRAb (IU/L)	0.81	0.67	<0.30	NA	0.3-1.75

Table 1: Thyroid profile on the day of admission and on the 30th day of treatment.

Discussion

Despite recent advances in neuroimaging, the etiology of oculomotor nerve palsy remains unknown in some cases. Here the two cases, after excluding common causes such as diabetic ophthalmic nerve palsy, aneurysm compression, brainstem cerebrovascular disease, and tumors, combination of clinical symptoms and thyroid function tests, the final diagnosis fell on the hypothyroidism-related oculomotor nerve palsy.

Neither patient had typical symptoms of hypothyroidism, such as fatigue, weight gain, hypothermia, dry skin, and myxedema with facial fullness. These symptoms are neither sensitive nor specific to the diagnosis [1, 8]. Thyroid disease may also present first with neurological complications [9, 11-13], as in our two patients who both had symptoms of oculomotor nerve palsy as their first symptom. Therefore, neurologists frequently encounter patients with thyroid disease [11, 21]. When the first symptom is a neuropathy, it is often misdiagnosed. Thyroid hormone deficiency can affect both the central and peripheral nervous systems [9, 11-13, 21]. However, cases with oculomotor nerve palsy as the first symptom are rarely reported. Here we report two unusual cases of oculomotor nerve palsy caused by severe hypothyroidism.

We found no significant elevation of A-TPO in either case, and no significant reduction of Echogenicity on ultrasound, so Hashimoto's thyroiditis was ruled out. Thyroid-associated ophthalmopathy (TAO) is also a cause of binocular diplopia in

adults [18, 19, 21], most associated with Graves' disease. It is also occasionally seen in patients with Hashimoto's thyroiditis, primary hypothyroidism, and thyroid cancer, as well as in patients who have undergone neck radiation therapy [18]. It would be helpful to identify TAO as the cause of diplopia if any of these thyroid disorders were diagnosed prior to the development of acquired binocular diplopia. Additionally, the most affected muscles in TAO are the inferior rectus and medial rectus muscles. Instead, thyroid-stimulating hormone (TSH) receptor Ab levels have been reported to be correlated with disease activity [18].

For hypothyroidism-associated oculomotor neuritis, as mentioned in the literatures [4, 18], is characterized by an enhanced oculomotor nerve signals seen on cranial MRI. In treatment, high-dose steroid hormone therapy will show good results [19, 14, 15, 20, 21]. Importantly the symptoms are not correlation with a decrease of thyroid hormones [4]. In our cases, the most obvious abnormality was the increase in A-TG. Even after one month of treatment with thyroid hormone the symptoms completely resolved, however, the A-TG antibodies did not decrease meaning that the relief of ophthalmoplegia symptoms was not related to the concentration of thyroid antibodies, which may suggest to some extent that the disease is due to hypothyroidism rather than an immune-mediated cause. It also further implies that the symptoms of oculomotor nerve palsy in the two cases were closely associated with a decrease in serum thyroid hormone concentrations. Complete resolution of symptoms was achieved with thyroid hormone replacement therapy. This is consistent with previous reports of oculomotor nerve palsy associated with hypothyroidism [1, 3].

When it comes to treatment, thyroid hormone replacement therapy was used in both cases, although glucocorticoids were also added in them both. Patients with idiopathic ophthalmic nerve palsy, as reported in other clinics, have responded well to steroids [7], but the mechanism is unclear; indeed, there is no clear evidence in this report to support a clear relationship between treatment outcome and glucocorticoids. This kind of oculomotor nerve palsy has been reported to occur in an idiopathic manner in healthy adults but can often resolve within a few months [18-21]. In some cases, it can persist. However, the authors emphasize that the need for steroid treatment requires a detailed diagnostic work-up.

We considered our cases of oculomotor nerve palsy was due to hypothyroidism. The exact pathogenesis of primary hypothyroidism-associated oculomotor nerve palsy is not known. Several possible pathogenetic mechanisms have been mentioned in the literature. First, thyroid hormones are important for regulating metabolic processes and maintaining cellular functions, especially in the central nervous system and peripheral nervous system [8, 9, 14]. Significantly reduced thyroid hormone levels leading to Schwann cell or neuronal dysfunction may be one of the key causes [8, 9]. Secondly, although rarely addressed in the literature, we believe that the pathogenesis is related to the action of T3 on adrenergic receptors. Both cases had significantly reduced levels of T3 at the presentation. One of the important functions of T3 is to enhance the response of β-adrenergic receptors [16]. We know that alpha and beta receptors are distributed both internally and externally in the eye. β1-adrenergic receptors are the predominant subtype in the oculomotor muscle. The interaction between α2 and β1 receptors in the upper eyelid retractor muscle may be important in controlling the position of the upper eyelid and may explain the impairment of eyelid coaptation in hypothyroidism. Damage to certain elements of the sympathetic nervous system can inhibit this muscle and cause the phenomenon of eyelid ptosis, which has similarities to Horner's syndrome caused by sympathetic neuropathy [16, 17].

Therefore, we supposed that thyroid hormone replacement therapy may be an effective treatment for primary hypothyroidism-related oculomotor nerve palsy. Our subsequent follow-up observed thyroid hormone levels in both patients remained largely within the normal range and that oculomotor nerve palsy did not recur. Therefore, maintaining normal thyroid hormone levels may be essential to prevent recurrence of occulomotor nerve palsy [21].

In addition, case 1 patient had significantly increased protein in the CSF with normal cell counts, consistent with previous reports of CSF changes in patients of the hypothyroidism with multiple cranial neuropathies [3]. Previous studies have shown that CSF protein abnormalities are associated with significantly lower thyroid hormone levels, but not with the presence of thyroid antibodies, which may suggest that the elevated CSF protein is due to blood-brain barrier (BBB) damage rather than to autoimmune process [5, 6]. An experimental study in dogs confirmed that dogs with chronic hypothyroidism induced by I^{131} administration had significantly elevated CSF protein levels compared to normal controls. And serum vascular endothelial growth factor and S100-B were found to be significantly elevated in the experimental group, suggesting that vascular endothelial and glial dysfunction may lead to a disruption of the BBB, resulting in increasement of CSF proteins [5, 6].

Both of our patients had mildly elevated serum CK values, but neither of them showed muscle weakness. According to previous studies, 57-90% of patients with hypothyroidism have elevated serum levels of muscle enzymes, especially CK [7, 10], and most of them will have muscle symptoms such as muscle stiffness, myalgia, cramps, and fatigue. However, elevated serum CK values are not necessarily associated with the severity of myopathy symptoms [7].

To this point, although we cannot completely exclude that common immune factor as the underlying mechanism, based on

the course of the disease, clinical presentation, and exam findings, we do not seem to support an autoimmune-mediated mechanism.

Finally, we would like to address the carpal tunnel syndrome of case 1 [15, 21] which is the most common mononeuropathy in hypothyroidism and whose pathogenesis may be the deposition of acidic mucopolysaccharides in the median nerve and surrounding tissues caused by hypothyroidism, which compresses and produces symptoms [11, 21]. His hypothyroidism was identified shortly before his initial presentation, and he underwent thyroid hormone replacement therapy. Carpal tunnel syndrome also resolved due to surgical treatment. However, the patient discontinued the medication on his own resulting in a recurrence of impaired hypothyroid function.

In summary, combining our report with previous literature, we précis the features of this type of disease as follows: oculomotor nerve palsy with pupillary involvement; markedly reduced thyroid hormone levels and elevated thyroid antibodies, especially A-TG, which may be accompanied by elevated CK and abnormally elevated protein in CSF; no abnormalities in cranial imaging; and effective thyroid hormone replacement therapy. Our report suggests that clinicians should be aware that hypothyroidism may be an etiology of oculomotor nerve palsy, which may help in the diagnosis and differential diagnosis. It is reasonable to assess thyroid function in patients with unexplained oculomotor nerve palsy.

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