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Case Report

Tolosa-Hunt syndrome with general myasthenia gravis involvement

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Tolosa-Hunt syndrome is an uncommon disease that exhibits unilateral periorbital pain or headache, accompanied by cranial nerve palsies. Myasthenia gravis is an acquired immune system disease involving the neuromuscular junction. One rare case of Tolosa-Hunt syndrome combined with ocular myasthenia gravis had been reported in the literature, but not general myasthenia gravis. We present a patient with a probable coincidence of Tolosa-Hunt syndrome and general myasthenia gravis. A 63-year-old male exhibited episodes of unilateral headache with double vision, bilateral ptosis, vision decrease in the left eye and left facial hypoesthesia, muscle weakness in limbs and neck. The muscle weakness was fluctuating and could be relieved by rest. Blood analysis, cranial magnetic resonance imaging, magnetic resonance angiography/venogram) and orbit/mediastinum computed tomography demonstrated no abnormalities. Serum myasthenia gravis related antibodies detection showed positive titin-antibodies and ryanodine receptor antibodies. Corticosteroid and pyridostigmine bromide treatments were effective. Each of the patient's symptoms had almost disappeared at the third-month follow-up. We speculate on the etiology of Tolosa-Hunt syndrome with general myasthenia.

Keywords

Tolosa-Hunt syndrome; myasthenia gravis; corticosteroids; headache; ptosis; neuroimmunology; ophthalmoplegia

1. Introduction

Tolosa-Hunt syndrome (THS) is a nonspecific inflammation disorder in the cavernous sinus, superior orbital fissure, or orbit, which causes periocular headache and ophthalmoplegia. Apart from cranial nerves for ocular movement, II, V, VII, VIII cranial nerves are sometimes also involved. THS has prompt responses to corticosteroids. THS may recur. Its pathogenesis may be related to viral infection and immune deficiency (Hunt et al., 1961). Myasthenia gravis (MG) is an auto-immune disease located at the neuromuscular junction, of which the pathogenesis is associated with the production of autoantibodies (Hehir and Silvestri, 2018; Pasnoor et al., 2018). The typical clinical feature of MG is skeletal muscle fatigue. It usually intensifies in the evening hours and eases after rest. At present, there is a case of THS combined with ocular muscle MG (Majumdar et al., 2017), but the combination of this with general MG has not been reported in the literature. Here we report a rare case of probable coincidence of THS with general MG, which exhibits periorbital headache with bilateral ptosis, limbs, and neck muscle weakness.

2. Case Report

A 63-year-old male was admitted to our hospital complaining of a headache, double vision, and blurred vision of the left eye for the last month. The pain was mainly in the left retro-orbit. It was initially an intermittent stabbing pain, it then gradually became continuous. Drooping eyelids accompanied left facial numbness, and visual loss appeared around 3-4 days after the headache. During hospitalization, the patient gradually showed weakness in the neck and proximal limbs, which was able to be relieved by rest. Complaints such as difficulty in chewing, swallowing, and nasal voice was absent. It is worth mentioning that he experienced similar orbital pain and monocular ptosis, blurred vision, but no diplopia four months before his admission. The symptoms disappeared in a few weeks with some pain medication. The patient had no history of headaches, diabetes, thyroid disorders, or other genetic diseases.

Examinations revealed blepharoptosis, restrictions in up- and downward movements of both eyes, decreased vision of the left eye, hypoesthesia over the first division of the left trigeminal nerve. Other cranial nerve examinations were normal. The strength of the neck and proximal limb muscles decreased (++). Fatigue test (+); Neostigmine test (+); Repetitive nerve stimulation (RNS) (-); Serum MG-related antibodies detection: AChR-Ab (-), muscle-specific kinase receptor antibody (MuSK-Ab) (-), ryanodine receptor antibody (RyR-Ab) (+), titin antibody (titin-Ab) (+). Computed tomography (CT) scan of the mediastinum was normal. There were no significant abnormalities with the orbit CT or the cranial magnetic resonance imaging (MRI) (Fig. 1) and magnetic resonance angiography/venogram (MRA/V). Hemogram and biochemistry, including the glucose level and thyroid function, were within normal ranges.

The patient was diagnosed with a probable coincidence of THS with general MG, and the treatment was started with dexamethasone 10 mg intravenously/day. After 5 days, the headache had

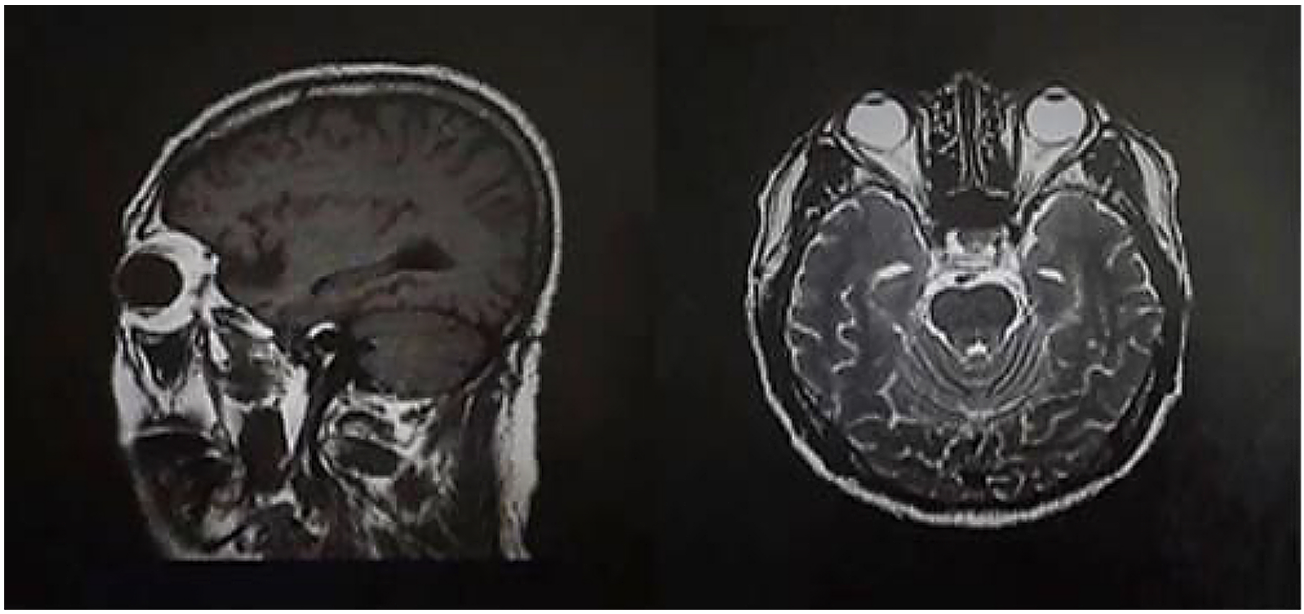

Figure 1. Sagittarius T1 and axial T2 scan of cranial MRI on November 2018. There was no evidence to explain the symptoms.

disappeared, vision decrease, ptosis, and left facial hypoesthesia had improved, while limbs and neck muscle weakness remained. On day 6, the patient appeared temporarily short of breath in the afternoon, which might have been due to the side effect of corticosteroid. He was suggested with 20 mg prednisone orally/day and 60 mg pyridostigmine bromide three times/day, and the shortness of breath did not re-occur. At the first month follow-up, significant improvements were noticed in terms of ptosis, diplopia, skeletal muscle weakness, and he initiated steroid tapering. The patient's condition was deemed almost completely normal at the third-month follow-up.

3. Discussion

For our patient, the unilateral periorbital headache was the main complaint accompanied by double vision, drooping eyelids, decreased left eye vision, and left face sensation. Cranial nerves II, III, V1 were involved in examinations, and corticosteroid treatments were effective. These fulfill the International Classification of Headache Disorders (ICHD)-2 diagnosis criteria of THS, although the head MRI was normal (İlgen Uslu and Özkan, 2015). However, the latest ICHD3/3beta criteria require granulomatous inflammation on MRI or biopsy, which is questioned by some scholars (IHS, 2018). They argued that a negative MRI does not rule out THS, and biopsy is not easy to obtain a positive pathology due to the lesion location, so neither MRI nor biopsy should be a must for diagnosis (IHS, 2018; Majumdar et al., 2017). Zhang et al. (2014b) reviewed 77 cases of THS from 2003-2013 and found 47.8% of patients had normal MRI. In another report, "Benign THS" was diagnosed in 57% of patients since MRI findings did not show inflammation (Hung et al., 2013). Therefore, in our case, probable THS was diagnosed. Considering the similar symptoms, the patient had four months before admission, and we view this as a recurrent THS with binocular involvement.

However, in our case, THS could not explain the loss of strength in the neck and limbs. The muscle weakness was fluctuating and could be relieved by rest, which is consistent with the characteristics of MG. Serum MG antibodies of this patient were shown as AChR-MuSK- Titin+ RyR+. Although the antibody of Titin+ and/or RyR+ may not serve as a diagnostic index for MG, but as a serological marker of MG, Titin-Ab has a very high specificity in MG and is hardly detected within healthy and non-MG patients (Chen et al., 2004). 27% of MG patients with AChR were found Titin+ (Chen et al., 2004). Titin-Ab and RyR-Ab were previously thought to be associated with thymoma. Recent studies revealed that the positive rates of Titin-Ab in late-onset (over 40 years old) male MG patients and in MG patients with thymoma were broadly similar. MG with thymoma might be AChR+ Titin+ RyR+, which is more severe in clinical manifestation.

The etiology of THS is unclear. The hallmark of this disease is nonspecific granulomatous inflammation characterized by the infiltration of lymphocytes and plasma cells of the cavernous sinus and/or superior orbital fissure (Kwan et al., 1988; Lutt et al., 2008). What incites the inflammatory reaction is still unknown. Cytomegalovirus (CMV) and actinomycosis infection have been reported to be involved (Mandrioli et al., 2004; Okawa et al., 2013). MG is an auto-immune disease mediated by AChR-Ab and can be worsened or induced by inflammation. However, no specific viruses or other pathogens have been proved to be related (Gilhus et al., 2019). After the body is infected with viruses or other nonspecific infection, B cells produce AChR-Ab in the abnormal thymus, thus causing cross-reaction between antibodies in myoid cells and postsynaptic membrane, resulting in transmission disorders of the neuromuscular junction (NMJ) (Gilhus et al., 2019). HIV and Hepatitis B combined with MG have been reported (Hung et al., 2011; Stubgen, 2010). Although no common specific pathogen of these two diseases has been found yet, it is possible that in some genetically heterogeneous individuals, the same virus or nonspecific factors might, at the same time, attack both thymus and cavernous sinus/orbital area, followed by a series of inflammatory or auto-immune reactions.

Another possibility is that, in some cases, THS might be one of the manifestations of an underlying auto-immune phenomenon, as mentioned by Arthur et al. (2020). They found that among 44 THS syndrome, 7% (3/44) of them with other auto-immune diseases may indicate the potential auto-immune phenomenon of THS syndrome (Arthur et al., 2020). Ocular MG combined with THS has been reported (Majumdar et al., 2017), while in our case, it is general MG with THS. Weather THS is a part of the auto-immune phenomenon involved in MG that needs further investigation. Arthur et al. (2020) also suggest that immunotherapy may prevent recurrences of THS.

With the recurrence rate being 50%, THS manifests itself as monocular or binocular involvement when relapsing (Zhang et al., 2014a). So primarily high-dose steroid pulse therapy is recommended. However, for THS complicated with general MG, especially when throat and respiratory muscles are involved, a high-dose steroid pulse treatment might lead to a myasthenic crisis. It is therefore advised that when the patient is diagnosed with such a complication of two diseases, incremental small-dose steroid therapy is more rational. Closely timed follow-ups and adjustment of steroid dosage should also be carried out concurrently (Zhang et al., 2014a).

Author contributions

Lu Li is responsible for literature research & drafted the literature; Zhe Wang is responsible for manuscript preparation; Ming-Ou Lu is responsible for the guarantor of integrity of the entire study, manuscript preparation & editing & review. All authors are approved in this manuscript.

Ethics approval and consent to participate

The case report was approved by the First Affiliated Hospital of Dalian Medical University Ethics Committee.

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Conflict of Interest

The authors declare no conflict of interest.

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