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Azathioptrine in Refractory Tolosa-Hunt Syndrome: Two Case Report

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ABSTRACT

Introduction: Tolosa-Hunt syndrome (THS) is an inflammatory disease with painful ophthalmoplegia and unilateral periorbital headache as detailed by the International Classification of Headache Disorders, 3rd edition (ICHD-3). Azathioprine has been suggested as a second-line treatment in refractory THS when oral corticosteroid only gives a partial response. **Case:** Two cases of THS, 45-year-old and 41-year-old women with unilateral headache, drooping of the left upper eyelid, and diplopia. They presented with complete ophthalmoplegia and ophthalmic division of trigeminal nerve disturbance. Magnetic resonance imaging (MRI) showed thickening of the left cavernous sinus, suggesting THS, while the other was normal. Corticosteroid (prednisone 1-1.5 mg/day) was given orally for the first two weeks, and according to the Numeric Pain Rating Scale (NPRS), pain intensity was reduced from severe to moderate. As a second-line treatment, azathioprine (2 mg/kg/day) was given afterward, with a significant reduction in pain intensity and remission of ophthalmoplegia within seven days. Azathioprine was used as an immunosuppressive agent and was continued for another three months without any deterioration in neurological deficits. The levels of complement 3, 4 (C3, C4), and C-reactive protein (CRP) were normal in both patients, with a slight increase in erythrocyte sedimentation rate (ESR) and equivocal values on antinuclear antibody (ANA) results. Other differentials of THS were eliminated from history-taking, physical examination, and proper investigations. **Conclusion:** Azathioprine as a second-line treatment can be used instead of an oral corticosteroid for refractory cases of THS with fewer side effects. Complete remission of ophthalmoplegia and a significant reduction in pain intensity was obtained.

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INTRODUCTION

Tolosa-Hunt syndrome (THS) is caused by granulomatous inflammation in the cavernous sinus, superior orbital fissure, or orbit, and is characterized by unilateral pain in the orbital region associated with paresis of one or more of the third, fourth, and/or sixth cranial nerves as mentioned in the International Classification of Headache Disorders, 3rd edition (ICHD-3).[1]

The first patient who suffered from orbital pain on the left side, followed by ipsilateral progressive visual loss, complete ophthalmoplegia, and decreased sensation over the ophthalmic division of the trigeminal nerve, was reported by Tolosa in 1954. This is an idiopathic condition with a non-specific granulomatous inflammatory process in cavernous sinus/ superior orbital fissure.[2]

High-dose glucocorticoids are chosen as the first-line medication for THS due to its inflammatory pathology, but without sufficient evidence for the recommended dose, route of entry, and treatment duration. Tremendous glucocorticoid treatment is the prompt intention of orbital pain as diagnostic corroboration within 1-3 days.[3]

Although it is considered a benign condition, permanent neurologic deficits can occur, and relapses often require prolonged immunosuppressive therapy. Other immunosuppressants such as azathioprine, methotrexate, or radiation therapy may be employed in refractory cases or in patients not tolerating steroid therapy.[2,4]

As a diagnosis of elimination, THS should be carefully distinguished from more malignant causes of cavernous sinus involvement and painful ophthalmoplegia. At this moment, we present two case reports of successful refractory THS with azathioprine as the second-line treatment option.

CASE

The first case is a 45-year-old woman with an abrupt onset of headache on the left side and drooping of the left upper eyelid since a month ago, followed by double vision. Periorbital headache extends retro-orbitally into the frontal and temporal regions with severe intensity. There was no history of vision loss. She was conscious, oriented, and afebrile; her pulse was 82 beats per minute, her blood pressure was 130/90 mmHg, and other mental and physical examinations were normal. On left eye examination, left-sided ptosis, a dilated non-reactive pupil without pupillary reflex, and complete ophthalmoplegia were found.

The right eye was normal. Paraesthesia was present over the left periorbital/forehead region, suggesting left-sided trigeminal nerve involvement. Other cranial nerve examinations were normal. Laboratory results were normal (C3 94.1, C4 25.8, and CRP 0.1), but the ESR was increased by 31 mm/hr in the first hour. The ANA test was found to be negative. The brain MRI was normal (Figure 1). Other differentials of cavernous sinus entanglement were eliminated from history taking, physical examination, and proper investigations. Oral corticosteroid (prednisone 1-1.5 mg/day) was administered for 14 days, with a partial response in the first week and a reduction in headache from severe to moderate (NPRS 8 to 4), but left ocular palsy persisted. Azathioprine (2 mg/kg/day) was given afterward, with a reduction of headache from moderate to mild (NPRS 4 to 2) and remission of ophthalmoplegia after one-week of treatment.

The second case is a 41-year-old woman with abrupt onset drooping of the left upper eyelid and a left-sided headache two weeks ago, with double vision. With severe intensity, the headache was constant, unilateral, left-sided, periorbital, extending retro-orbitally into the frontal and temporal regions. There was no history of vision loss. She was afebrile, pulse 78 beats/min, blood pressure 110/80 mmHg, other general physical examinations were normal. On left eye examination, there was left-sided ptosis with a dilated non-reactive pupil, without pupillary reflexes and complete ophthalmoplegia.

The right eye was normal. In addition, paraesthesia was present over the left periorbital/forehead region, suggesting left-sided trigeminal nerve involvement. Other cranial nerve examinations were found to be normal. The laboratory result for ESR increased 29 mm/hr in the first hour, while the others were normal (C3 103, C4 42.8, and CRP 0.1). ANA testing was found to be negative. Brain MRI showed thickening of the cavernous sinus, isointense in T1WI, supporting THS (Figure 2). Oral corticosteroid (prednisone 1-1.5 mg/day) for 14 days was given with partial response in the first week and a reduction of headache from severe to moderate (NPRS 9 to 6), but ocular palsy persisted. Azathioprine (2 mg/kg/day) was given afterward and showed a good response after 1-week of treatment with a reduction of moderate to mild headaches (NPRS 6 to 2) and a complete remission of ophthalmoplegia.

DISCUSSION

THS is caused by granulomatous inflammation in the cavernous sinus, superior orbital fissure, or orbit with unilateral orbital or periorbital pain accompanied by paresis of one or more of the third, fourth and/or sixth cranial nerves. Diagnostic criteria for THS according to ICHD-3:[1]

A. Unilateral orbital or periorbital headache fulfilling criteria C.
B. Both of the following:
   1. granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy
   2. paresis of one or more of the ipsilateral third, fourth and/or sixth cranial nerves
C. Evidence of causation demonstrated by both of the following:
   1. headache is ipsilateral to the granulomatous inflammation
   2. headache has preceded paresis of the third, fourth and/or sixth nerves by 2 weeks, or developed with it
D. Not better accounted for by another ICHD-3 diagnosis.

The association of the fifth nerve (commonly ophthalmic division), seventh or eighth nerve has been reported in some cases of THS, occasionally accompanied by the involvement of sympathetic innervation of the pupil. Other differentials of painful ophthalmoplegia, such as tumors, vasculitis, basal meningitis, sarcoid, or diabetes mellitus, were ruled out. Corticosteroids were chosen as the first-line treatment to reduce pain and paresis from THS. [1,5–7]

Pain intensity was assessed with the Numeric Pain Rating Scale (NPRS). Zero usually characterizes "no pain at all," whereas 10 characterizes "the worst pain ever possible." The feasibility of NPRS with good obedience has also been confirmed, as it is easily manageable verbally and it can be used in telephone interviews.

THS responded well to corticosteroid treatment, but no standard dose has been established. Faster improvement of symptoms was seen in younger patients, and retro-orbital pain has been reported to settle within 72 hours of steroid treatment.[7,8,9]

THS is a benign condition, but permanent neurologic deficits can occur, with recurrences and often requiring prolonged immunosuppressive therapy. In refractory cases, azathioprine, methotrexate, or radiation therapy may be considered for partial response to steroid treatment.[4,10,11] The use of immunotherapy to prevent recurrences is still controversial. Oral azathioprine 50 mg twice daily (2 mg/kg/day) was given with close monitoring of the complete blood count, liver, and renal function tests. The observational study of azathioprine as an immunosuppressant for central serous retinopathy treatment associated with THS signified that azathioprine could be used as an alternative therapy for THS. [11,12,13]

Azathioprine is an immunosuppressive agent and an antimetabolite prodrug. It is an imidazolyl derivative of 6-mercaptopurine in the body that acts by blocking purine metabolism and may impede the synthesis of DNA, RNA, and proteins. It may also inhibit cellular metabolism and mitosis. The course of action is appropriate due to a combination of thiopurine analogs into the DNA structure, causing chain termination and cytotoxicity.[11,14,15]

The use of azathioprine in our cases has given significant results. Pain intensity measured by NPRS was reduced from moderate to mild (NPRS 4 to 2 in the first case and NPRS 6 to 2 in the second case), followed by complete remission of ophthalmoplegia

CONCLUSION

Tolosa-Hunt syndrome (THS) presented with unilateral headache and painful ophthalmoplegia. Azathioprine can be chosen as a second-line treatment with good results instead of an oral corticosteroid for refractory cases of THS with fewer side effects. It gives significant depletion in pain intensity followed by a complete remission of ophthalmoplegia.

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ATTACHMENT

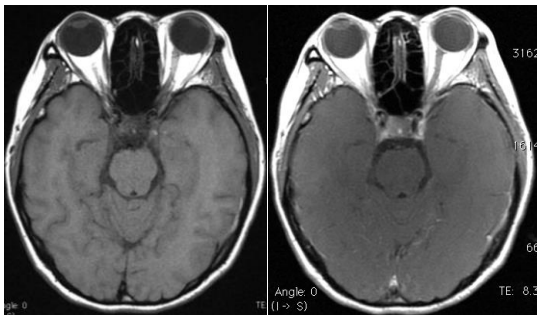

Figure 1. Brain MRI was normal.

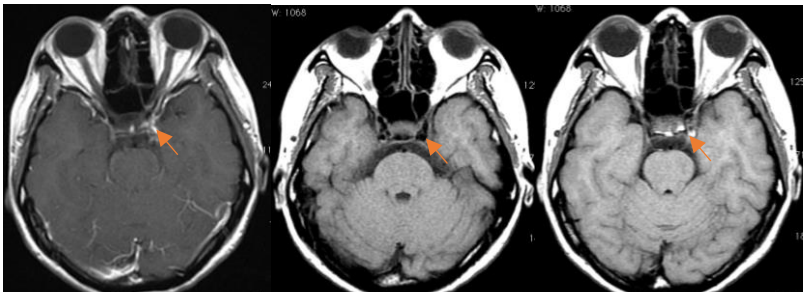

Figure 2. Brain MRI showed thickening of the cavernous sinus, isointense in T1WI, supporting THS.

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