Inflammatory Involvement of the Hypophysis in Tolosa-Hunt Syndrome

Choichi Hida, Teiji Yamamoto, Kazuhiro Endo, Yoshihiro Tanno, Tasuku Saito and Tetsuro Tsukamoto

We report a case of painful ophthalmoplegia (Tolosa-Hunt syndrome), which was complicated with diabetes insipidus (DI) and pituitary-adrenal axis hypofunction. A 42-year-old man hospitalized for left orbital pain and impairment of left cranial nerves III, IV, V, VI, developed diabetes insipidus during the corticosteroid treatment. Neuroimaging studies disclosed a thickened, highly contrast-enhanced pituitary stalk, swollen pituitary gland and widened left cavernous sinus up to the superior orbital fissure, which were accompanied by diabetes insipidus and hypofunction of the pituitary-adrenal axis. These were indicative of an extension of granulomatous inflammation of the cavernous sinus to the pituitary portal system and the gland itself.

Key words: painful ophthalmoplegia, granulomatous hypophysitis, diabetes insipidus, anti-phospholipid antibody, hypopituitarism

Introduction

Tolosa-Hunt syndrome is characterized clinically by unilateral retro-orbital pain, ophthalmoplegia and responsiveness to corticosteroids, but relapse is notoriously common. Clinical, neuroradiological and some pathological studies point to a nonspecific granulomatous inflammation in the region of the cavernous sinus and superior orbital fissure, but the pathogenesis remains unknown. We treated a case of Tolosa-Hunt syndrome that was complicated with diabetes insipidus and pituitary-adrenal hypofunction during the course of treatment. Since neuroimaging studies indicated inflammatory involvement of both the pituitary stalk and the pituitary gland in an otherwise classical case of Tolosa-Hunt syndrome, this case provides insight into the pathogenesis of this particular disorder.

Case Report

A 42-year-old home interior decorator noted diplopia on the morning of October 30, 1991 and the left eye movement (left abduction paresis) was found impaired by an ophthalmologist. From this time on, the patient began feeling dull aching behind the left eye. Diplopia was gradually worsened, and from March 10, 1992, polydipsia and polyuria abruptly appeared, which necessitated intake of a large volume of fluids. Since general malaise, pain over the left forehead and nausea were intolerable, the patient was admitted to our neurology service on March 17, 1992. Urine volume at the time of admission had returned to normal, however.

Physical examination on admission revealed an obtunded man with dry skin. The blood pressure was 180/120 mmHg; pulse rate 80/min, regular and body temperature 37.1°C. Mild congestion and edema of the left conjunctiva bulbi were noted. There was pain and tenderness over the left forehead but the eyeball itself was neither tender nor tense. Orbital bruit was not audible.

Neurologically, there were no meningeal irritation signs. Mentally he was clear and higher cerebral functions were unremarkable. The cranial nerves disclosed visual acuity of oculus dexter (O.D) = 0.1 (1.2X–3.0), oculus sinister (O.S) = 0.2 (0.6X–1.75). The visual field was normal to confrontation testing. The left pupil was 2.5 mm in diameter, irregularly round and sluggishly reactive to light but the right pupil was 2.5 mm, round and normally reactive. Funduscopic examination revealed normal discs, maculae and retinal vasculature without exudate or hemorrhage. He was unable to open the left upper eyelid. A marked impairment in extraocular movement was observed on the left eye to all directions, indicating paralysis of the oculomotor and abducens nerves; the trochlear nerve was not involved, however, as attempted downward gaze revealed depression and intorsion. Convergence was impossible. Right eye movement was normal. There was a decrease in superficial sensation over the left V-1 distribution with diminished corneal

From the Department of Neurology, Fukushima Medical College, Fukushima
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Reprint requests should be addressed to Dr. Choichi Hida, the Department of Neurology, Fukushima Medical College, 1 Hikarioka, Fukushima 960-12

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reflex. The remainder of the cranial nerves were normal. Motor, sensory and reflex systems were unremarkable.

The results of blood and biochemical studies indicated active systemic inflammatory process; white blood cell count (WBC) 11,000/mm³, (eosinophils 1.0%), erythrocyte sedimentation rate (ESR) 23 mm/1 hour, 47 mm/2 hours and C reactive protein (CRP) 1.8 mg/dl. Prothrombin time and activated partial thromboplastin time were within the normal range. Venereal disease research laboratory test (VDRL) was negative. Serum angiotensin converting enzyme was in the normal range. Antinuclear, anti-DNA, anti-RNP, anti-SS-A, anti-SS-B and anti-pituitary autoantibodies were all negative. Anti-cardiolipin IgG antibody was, however, positive (3.0; normal <1.0), but anti-cardiolipin IgM antibody was less than 0.5 (normal <1.0). Lupus anticoagulant was not detected. Anti-HTLV-1 and anti-HIV antibodies were negative. Tuberculin skin test was strongly positive (28×25/67×47 mm with a blister), but acid-fast staining of the sputa and sediments of gastric juice revealed no bacilli, and repeated cultures of these specimens were negative for tuberculous bacilli. A 75g-oral glucose loading test showed borderline intolerance. Thyroid functions revealed; T3 1.3 ng/dl (normal range 0.8-1.8 ng/dl) and T4 8.1 μg/dl (normal range 4.0-12.0 μg/dl); thyroid antibodies, microsome hemagglutination (MCHA) and thyroglobulin hemagglutination (TGHA), were negative.

With regard to the pituitary posterior lobe and pituitary-adrenal axis functions, the baseline antidiuretic hormone (ADH) was in a low-normal range (0.5 pg/ml, normal range; 0.3-4.2 pg/ml), adrenocorticotropic hormone (ACTH) was as low as 4.4 pg/ml (normal range; 6.1-55 pg/ml), and plasma cortisol was consistently below 1.0 mcg/dl (normal range; 2.7-18.3 mcg/ml). The remainder of pituitary functions were: growth hormone (GH) 2.8 ng/ml (normal range; <5.0 ng/ml), prolactin (PRL) 40 ng/ml (normal range 5-27 ng/ml), luteinizing hormone (LH) 0.7 mIU/ml (male normal range; 1.1-8.8 mIU/ml), follicle stimulating hormone (FSH) 2.8 mIU/ml (male normal range; 1.8-13.6 mIU/ml), thyroid stimulating hormone (TSH) 0.03 μU/ml (normal range <10 μU/ml). Anterior pituitary cell antibodies (PCA) and antibodies for anterior pituitary cell surface membrane (PCSA) were negative.

Cerebrospinal fluid (CSF) was under normal pressure, protein was slightly elevated (50 mg/ml) and the cell count was normal. Pattern-shift visual evoked response showed a delay of P-100 (121 msec, normal <95.8±5.8 msec) by mono-ocular stimulation to the left eye but the right side was normal.

Plain X-ray films of the skull revealed a slight widening of the left superior orbital fissure, but the sella turcica appeared unremarkable. The contrast-enhanced computed tomographic scan (CT scan) revealed the cavernous sinus being clearly enhanced bilaterally; in particular the left side appeared broader up to the region of the superior orbital fissure (Fig. 1). Because of the diffusely enhanced intercavernous sinuses proper, pituitary diaphragm and stalk, together with the cavernous sinuses, it was difficult to discern each structure separately over the interclinoid plane. Above that level, a rather swollen, highly enhanced pituitary stalk was apparent. A small mucocele was attached to the dorsal surface of the sphenoid sinuses.

The coronal sections of the T1-weighted magnetic resonance imaging (MRI) showed the tightly-bulged lateral border of the left cavernous sinus but the signal intensities of the intracavernous structures did not differ from those of the counterpart. The cavernous segment of the left internal carotid artery appeared slightly narrow and displaced inferiorly. The pituitary gland was iso-intense on T1-weighted image and swollen, and it was difficult to distinguish the posterior lobe from the anterior lobe on horizontal MRI (sagittal images were not performed). Remarkable was the appearance of the pituitary gland that was like a snowman; the upper portion was herni-
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Figure 3. Coronal section of Gd-DTPA enhanced MRI shows that the bilateral cavernous sinus and pituitary gland were all homogeneously enhanced.

Figure 4. Digital subtraction orbital venography disclosed that the left superior ophthalmic vein is tortuous in its posterior segment and then tapers off posteriorly (arrows).

The relationship between plasma osmolarity and plasma-antidiuretic hormone (P-ADH) level. P-ADH was repeatedly low.

Clinical course

A 5-day course of pulse-dose methylprednisolone (1,000 mg/day) was given immediately after admission (March 27) in order to rescue the multiple cranial nerve palsies. Left orbital pain and blepharoptosis improved within a few days and the corticosteroid was switched to oral daily prednisolone (60 mg). However, from March 27, diabetes insipidus became apparent (average urine volume was 7,500 ml/day and the urine specific gravity was 1.005). The relationship between serum ADH and serum osmotic pressure shown in Fig. 5 indicated the presence of central diabetes insipidus. Diabetes insipidus responded promptly to 1-deamino-8-D-arginine-vasopressin (DDAVP) nasal spray with normalization of daily urinary output. When diabetes insipidus was suspected but not apparent; plasma ADH was 0.5 pg/ml when clinically overt, it was then markedly depressed to less than 0.2 pg/ml. The ADH level remained low for the next two months. ACTH had been low (4.4 pg/ml), however, following methylprednisolone therapy, it was in the low normal range. The value of cortisol was less than 1.0 mcg/dl before the treatment with methylprednisolone (May 24) and increased to 70 mcg/dl on April 3 during oral prednisolone administration when diabetes insipidus became apparent.

Serum osmotic pressure was on the order of 280 to 300 mOsm/l but urine osmotic pressure was markedly decreased (140 to 240 mOsm/l). After DDAVP administration, urine osmotic pressure increased to the order of 500 to 800 mOsm/l with reduction in urine volume. Prednisolone was gradually tapered to the alternative day dose and left ophthalmoplegia was greatly improved. Anti-cardiolipin antibody titers that had been 3.0 (IgG, normal <1.0) and 0.5 (IgM, normal <1.0) before the treatment were shifted to IgG 2.7 and IgM 1.5 on April 3 and then IgG 1.9, and IgM 1.7 on May 26. The patient was...
discharged on June 1 with only mild diplopia to lateral gaze. At the time of discharge, prednisolone was given (25 mg daily), and then slowly decreased to 15 mg for the subsequent 5 months. DDVAP was discontinued within a few months after discharge. Although serum ADH had been low (below 0.2 pg/ml), after having discontinued the DDVAP, the daily urine volume remained almost within the normal range. Serum ACTH, cortisol and urine 17-ketosteroid (17-KS) were within the normal ranges just before discharge. Other anterior pituitary functions were all in normal ranges except FSH which was slightly high. Six months later, he again developed painful diplopia and then incomplete external and internal ophthalmoplegia developed in a week on the right eye, however, without diabetes insipidus. A course of corticosteroid therapy was again given and symptoms gradually subsided in a few weeks.

**Discussion**

Although the pathogenesis remains unknown, Tolosa-Hunt syndrome is an granulomatous inflammatory disorder in the cavernous sinus and adjoining superior orbital fissure (1, 2) and the symptomatology is rather stereotyped. However, the case presented here is unusual in that diabetes insipidus and pituitary-adrenal hypofunction were complicated in an otherwise classical example of Tolosa-Hunt syndrome. To date only a few reports have described diabetes insipidus in association with this particular syndrome (3). MRI and CT imaging studies clearly delineated the inflammatory processes of the cavernous sinus and the extension of the inflammation into the pituitary stalk and the pituitary gland itself. The swollen, contrast-enhanced pituitary stalk, indicating the inflammation of presumably the highly-vascular pituitary portal system, was well-correlated with the occurrence of diabetes insipidus. Since corticosteroid had to be administered promptly, the pituitary functions were not fully worked up. However, a modest insufficiency of the ACTH-adrenal system was apparent. The simultaneous impairment of the pituitary stalk-posterior lobe and pituitary-adrenal axis appears to have obscured diabetes insipidus at the beginning of the disease but it was subsequently unmasked by the correction of corticosteroid deficiency. Important to note is that the central diabetes insipidus and decreased ACTH secretion were reversible in this case.

By neuroimaging studies, in this case it is certain that the pituitary stalk was involved in inflammation and thus the development of diabetes insipidus is well explained. The impairment of the pituitary-adrenal axis might have occurred at the same level as ACTH is regulated by hypothalamic corticotropin releasing factor (CRF) via the pituitary portal system. However, the gland itself appears to have also been involved by the inflammation, as far as neuroimaging studies are concerned. The precise distinction is, however, difficult in view of the lack of CRF evaluation. The primary inflammatory diseases such as lymphocytic hypophysitis and granulomatous hypophysitis are also possibilities (4, 5). However, lymphocytic hypophysitis is unlikely in the absence of anti-pituitary autoantibody and the evidence of inflammation in the surrounding cavernous sinus is obvious.

Granulomatous hypophysitis, the etiology of which is unknown, cannot be excluded without pathological verification. It is possible, however, that granulomatous hypophysitis might be the inflammation, the pathological process of which is not unlike that of Tolosa-Hunt syndrome. One of the causes of which might be thus the pituitary extension of indolent inflammation of the cavernous sinus or the inflammation may have begun and was confined to the pituitary gland and the stalk. The positively correlated anticardiolipin antibody titers with Tolosa-Hunt syndrome imply that autoimmune-mediated inflammation might play a role in Tolosa-Hunt syndrome. Although only a few reports are available on the association of this disorder and anti-phospholipid antibodies (6), accumulation of similar cases may further elucidate the causal relation of this combination (7–10).

**References**