Pituitary Hyperplasia in Tolosa Hunt Syndrome: Demystifying the Great Mimic

Tolosa Hunt Syndrome (THS) has been typified by unilateral headache with periorbital pain and weakness of the third, fourth, or sixth cranial nerves, hypothesized to be secondary to granulomatous inflammation in the cavernous sinus, superior orbital fissure, or orbit. Additional features of THS described in the third edition of the International Classification of Headache Disorders (ICHD-3 beta version) emphasize either the simultaneous development of headache and cranial nerve palsies or an interval of a minimum of two weeks between both of them. Both radiological and biopsy-proven granulomatous inflammation of the cavernous sinus, superior orbital fissure, and ipsilateral ophthalmoplegia are required for diagnosing THS, with no better accountable diagnosis.[1] A great mimicker, THS remains essentially a diagnosis of exclusion as similar clinical presentations may be encountered due to neoplastic, vascular, inflammatory, endocrine, or infectious causes.[2] The literature demonstrates a paucity of pituitary involvement in THS. After a thorough literature search, we conclude that pituitary involvement in THS was not described earlier; the presence of clinical and radiological steroid responsiveness confirmed the diagnosis of THS without any other possible identifiable cause. The associated hypothyroidism complicated the clinical scenario; elevated levels of thyroid-stimulating hormone, the response of which to steroid therapy and positivity to anti-thyroid peroxidase antibodies, suggested primary hypothyroidism secondary to autoimmune thyroiditis.

A 35-year-old gentleman presented with binocular diplopia, accompanying retro-orbital pain, and a left-sided hemicranial headache for six weeks before presentation. The patient's medical history included hypothyroidism and hypercholesterolemia treated with a statin. The physical examination revealed severe global restriction of all left eye movements and pupil-sparing partial ptosis. Magnetic Resonance Imaging (MRI) brain revealed an intrasellar, 11 × 14 × 12-mm mass within the pituitary [Figure 1], with an asymmetric soft tissue prominence and enhancement of the left cavernous sinus. A complete hormonal workup revealed primary hypothyroidism (serum concentrations: thyroid-stimulating hormone >100 uU/ml; free T4: 0.42 microgram/dl; free T3: 120 ng/dl). The endocrinological assay showed normal levels of other hormones (ACTH 14.6 pg/ml; morning cortisol 280 nmol/l; prolactin 250 mU/l, LH 32.21 U/l, FSH 71.66 IU/l; urine specific gravity 1.015 g/l). Complete blood count, liver and renal functions, C-reactive

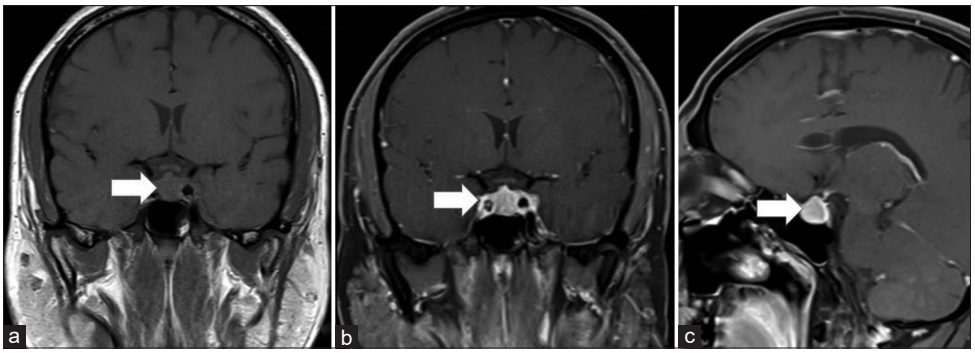

Figure 1: (a) T1-weighted image (coronal section) showing bulky left cavernous sinus with isointense signal, (b) T1 fat sat post-contrast image (coronal) showing pituitary enlargement and asymmetric soft tissue prominence, and contrast enhancement in the left cavernous sinus, (c) Post-contrast T1-weighted sagittal image showing pituitary hyperplasia

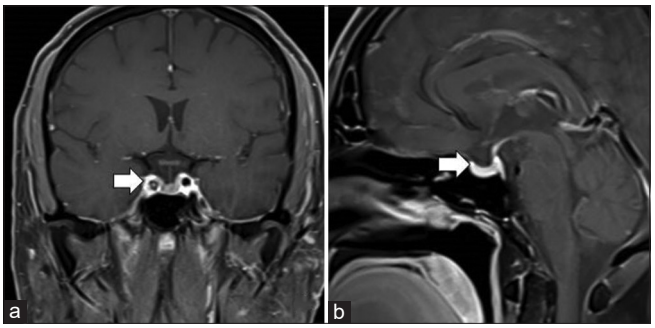

Figure 2: (a) Follow-up post-contrast T1-weighted image showing diminished pituitary size with resolution of left cavernous sinus contrast enhancement, (b) Follow-up post-contrast T1 weighted sagittal image showing resolution of pituitary hyperplasia

protein (2.91 mg/l), and Erythrocyte Sedimentation Rate (ESR) (20 mm/h) were normal. Serum IgG4, anti-nuclear antibody, anti-dsDNA, ANCA, HIV, Hepatitis B, C serology, and VDRL were negative. Serum angiotensin converting enzyme levels were within normal limits. Chest and abdomen Computed Tomography (CT) did not reveal any abnormalities. Cerebrospinal fluid studies were normal. He was treated with methylprednisolone intravenously for five days, followed by oral steroids. He completely improved and remained asymptomatic at four months of follow-up, with radiological reduction in the pituitary and cavernous sinus infiltrates on follow-up [Figure 2].

We report pituitary hyperplasia as a novel addition to the classical anatomical sites described to be involved in THS. Significant clinical remission, radiological regression, the biochemical response of hypothyroidism to steroid therapy, and reasonable exclusion of alternative etiologies confirm pituitary involvement secondary to THS.

A diagnosis of exclusion, THS encompasses granulomatous inflammation that is classically known to involve the cavernous sinus, superior orbital fissure, and rarely the orbital apex. Steroid-responsive headaches with painful ophthalmoplegia are characteristic of THS.[2] Making the correct diagnosis is vital because THS is exquisitely steroid-responsive, which defines the disease in retrospect after therapy.

Imaging plays a pivotal role in diagnosis. On MRI, there is an enlargement of the cavernous sinus with soft tissue that is T1 isointense, with a variable signal on T2, and consistent contrast enhancement, as seen in our case. A retrospective analysis of 53 patients demonstrated that involvement of the pituitary should raise suspicion of sinister alternative causes in a suspected case of THS.[3] Contrary to these observations, our case had additional pituitary hyperplasia. The only other case reported in the literature has been bilateral THS with involvement of the pituitary, where spontaneous regression was documented.[4] While THS is considered innocuous and has been shown to resolve spontaneously within a few weeks, morbidity from residual cranial nerve palsies can be disabling, which warrants immunosuppressive treatment.[2] Hence, we instituted early treatment with intravenous steroids that led to complete remission.

Another interesting observation that proved to be a confounding clinical scenario in our case was the presence of primary hypothyroidism, which was incidentally detected while investigating for pituitary involvement. However, prolonged primary hypothyroidism has been well known to cause pituitary hyperplasia consequent to excessive thyrotropin-releasing hormone from the hypothalamus due to loss of negative feedback.[5] Pituitary enlargement and elevated TSH levels can be seen in thyrotropin-producing pituitary adenoma, which can be radiologically differentiated, as discussed later. Central hypothyroidism is characterized by low serum T3 and T4 levels with an inappropriately low serum TSH concentration, while primary hypothyroidism demonstrates very high levels of TSH with low T4 concentrations, as seen in this case.[6] Concurrent anti-TPO positivity, which is invariably absent in hypothyroidism of central cause, pointed towards an autoimmune cause of primary hypothyroidism that showed a biochemical response to steroid therapy. A drastic reduction in TSH levels and a reduction of the requirement for a dose of levothyroxine at follow-up also suggest that hypothyroidism was probably autoimmune in origin. Infectious, vasculitic, and connective tissue disorders were ruled out as detailed in the investigations.

Pituitary hyperplasia has heterogeneous descriptions in the literature. It is usually described by an enlarged enhancing pituitary gland with a convex superior margin and sizes of more than 10 mm up to 15 mm. Lymphocytic hypophysitis and pituitary adenomas are usually difficult to differentiate. While the former shows a low T2 signal, parasellar dark T2 sign, and uniform smooth enhancement, pituitary adenomas show heterogeneously bright signal on T2 sequences with non-uniform contrast enhancement. Other differentials for pituitary hyperplasia include intracranial hypotension and dural-based meningiomas, which are easy to diagnose in the presence of associated imaging abnormalities.[7]

This case report highlights rare pituitary involvement in THS. Resolution of pituitary hyperplasia with steroid therapy confirms the diagnosis of THS in the absence of any alternative identifiable cause, and the association appears to be causal. Careful clinical examination and MRI interpretation circumvented the need for histopathological examination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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