

Trigemino-autonomic headache and Horner syndrome as a first sign of granulomatous hypophysitis

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ABSTRACT

Objective: To report a rare case of incipient granulomatous hypophysitis presenting by atypical trigemino-autonomic cephalalgia (TAC) and Horner syndrome.

Methods: The patient was investigated with repeated brain MRI, CSF examination, thoracic CT, Doppler and duplex ultrasound of the cerebral arteries, and extensive serologic screening for endocrine and autoimmune markers. Written informed consent was obtained from the patient for access to clinical files for research purposes and for publication.

Results: We present a middle-aged woman with a history of an autoimmune pancreatitis type 2 who had therapy-refractory TAC with Horner syndrome. Initial cerebral MRI showed only indistinct and unspecific signs of a pathologic process. A biopsy revealed a granulomatous hypophysitis. The symptoms disappeared after transsphenoidal subtotal resection of the pituitary mass and anti-inflammatory therapy.

Conclusions: This case elucidates that inflammatory pituitary diseases must be taken into account in case of atypical and refractory TAC, especially in patients with a history of autoimmune diseases. To our knowledge, the association between TAC accompanied by Horner syndrome and hypophysitis has not yet been described before. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e332; doi: 10.1212/NXI.0000000000000332

GLOSSARY

AIP-II = autoimmune pancreatitis type 2; **FT3** = free T3; **HPF** = high-power field; **TAC** = trigemino-autonomic cephalalgia; **VAS** = visual analog scale.

Hypophysitis is a rare inflammatory disease of the pituitary gland with an incidence of 1 in 9 million.¹ The pathogenesis of hypophysitis is not yet completely understood; however, in most cases, autoimmune inflammatory mechanisms seem to play a role.¹ Up to the last years, only a rough classification into granulomatous, lymphocytic, or xanthomatous subtypes was used. Recently, 2 new types, the IgG4 antibody-related hypophysitis and the secondary medication-induced hypophysitis, have been described.^{1,2} Typical clinical manifestations include endocrine abnormalities (e.g., diabetes insipidus, corticotroph deficiency, or hyperprolactinemia), visual disturbances, and headache. Oftentimes, patients describe migraine or tension-type-like headaches.³ By contrast, trigemino-autonomic cephalalgia (TAC) is rare. To our knowledge, a relationship of TAC to hypophysitis has been described only once before.⁴

Here, we report a patient with TAC refractory to medical therapy and Horner syndrome as a first sign of autoimmune hypophysitis.

PATIENT DESCRIPTION A 44-year-old woman with a history of an isolated biopsy-proven autoimmune pancreatitis type 2 (AIP-II) presented to our department with sharp left-sided occipital headache refractory to medical therapies. She reported nocturnal headache attacks with a duration of 1–2 hours and an

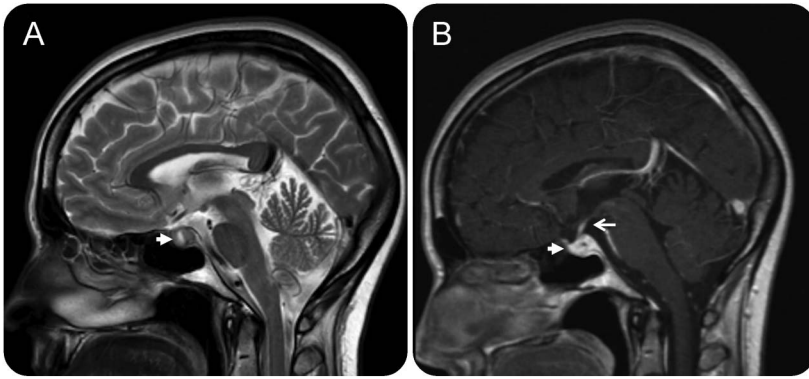
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Figure 1 Initial and early head MRI

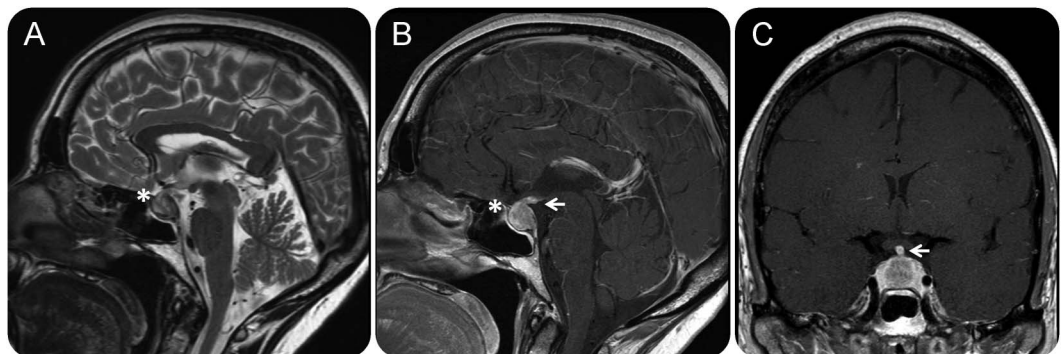


(A) Initial head MRI on admission; sagittal T2-weighted scan of the brain revealed an enlarged pituitary gland with a central T2-hyperintense abnormality (closed arrow). Immediate follow-up contrast-enhanced MRI (B) showed intensive enhancement of the pituitary gland and infundibular stalk (open arrow) suggestive of inflammation. Furthermore, the sellar mass is amplified and seems swollen.

intensity of 10/10 on the visual analog scale (VAS). These attacks were accompanied by conjunctival injection and lacrimation of the left eye, facial swelling, and underlying bilateral temporal persistent throbbing headache (VAS 5–6/10), present for 3 weeks before admission. The patient had a history of infrequent tension-type headache (4–5 episodes per year). There was no history of alcoholism, smoking, hypertension, diabetes mellitus, or head trauma. Clinical examination revealed no abnormalities. A preceding therapy with nonsteroidal anti-inflammatory drugs and tilidine (50 mg/d) did not relieve pain. An outpatient cerebral MRI examination was reported as normal. Analysis of the CSF revealed 7 lymphocytes cells/ μL but no further pathologic findings. All other tests, including blood tests (including serum antineutrophil cytoplasmic antibody) and Doppler

and duplex ultrasound of the cerebral arteries, were normal. An oxygen therapy with 4 L/min during pain attacks was unsuccessful. Under symptomatic therapy with pregabalin (150 mg/d), duloxetine (30 mg/d), and ibuprofen (600 mg on demand), the headache resolved completely. However, ten days later, the patient was readmitted because of recurrence of the headache and a new right-sided Horner syndrome. Anhidrosis was not observed. Visual acuity, color vision, visual fields, fundoscopy, and remaining physical examinations were normal. Carotid artery dissection, brachial plexus, and lung apex pathologies were excluded. Reevaluation of the initial head MRI revealed a suspicious T2-hyperintense central lesion in an enlarged pituitary gland (figure 1A). A follow-up MRI including dynamic T1w-enhanced sequences of the pituitary gland confirmed signs of a pathologic intrasellar mass (figure 1B). On further history taking, the patient reported a premature menopause in her early forties. Laboratory investigation of the hypothalamo-pituitary axis revealed an increased prolactin (figure e-1 at Neurology.org/nn) and slightly decreased luteinizing and follicle-stimulating hormone levels. Both thyroid-stimulating hormone and free T3 (FT3) were decreased, and no antithyroid antibodies were detected. Moreover, water deprivation test, investigating posterior pituitary function, was pathologic. Antipituitary antibodies to anterior and posterior lobes and autoantibodies to vasopressin cells were negative. After a methylprednisolone pulse (6 \times 125 mg), the headache and Horner syndrome disappeared. Two months later, a follow-up MRI yielded an increase of the sellar mass (figure 2, A–C). At the same time, the severe headache episodes recurred. After microneurosurgical resection of the pituitary mass lesion via transnasal-transsphenoidal approach, histology revealed a mixed cellular inflammatory lesion with eosinophilic granulocytes,

Figure 2 Follow-up head MRI

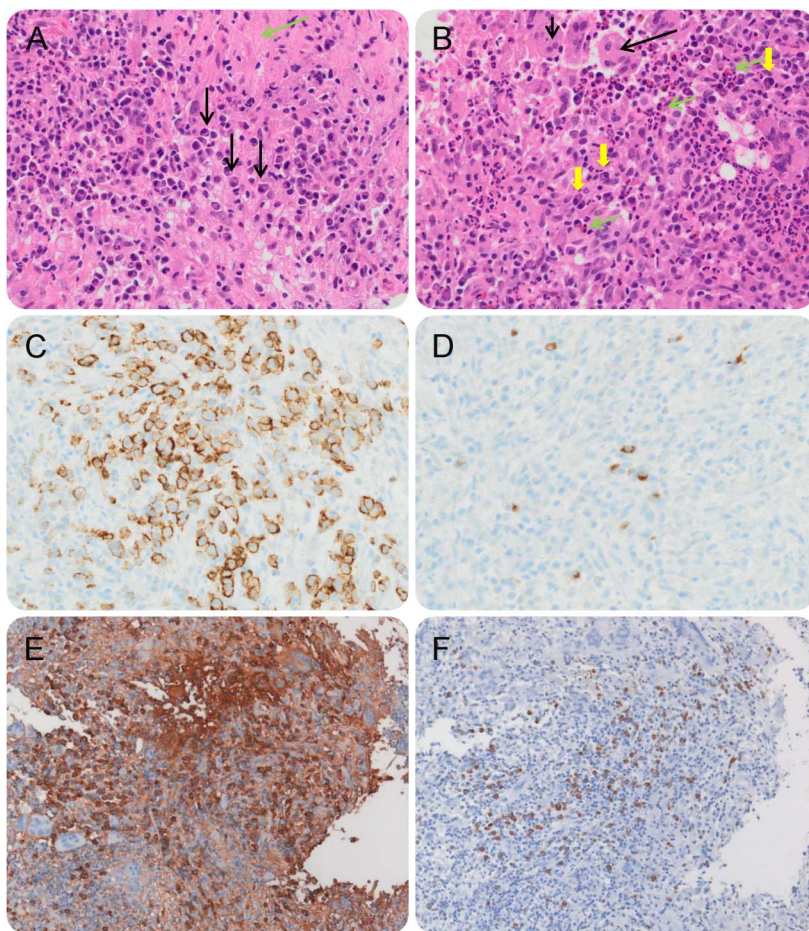


Two months later, a further MRI yielded progressive pituitary gland enlargement (asterisk) on sagittal T2-weighted images (A) with a thickened stalk (open arrow), both enhancing on a contrast-enhanced T1-weighted sequence (B: sagittal and C: coronal view; 2-mm slice thickness).

giant cells, T- and B-lymphocytes, and groups of plasma cells. Histomorphology pointed to the existence of a granulomatous hypophysitis. Moreover, the number of IgG4-positive plasma cells focally reached >10 /HPF (high-power field), which is why an IgG4-associated hypophysitis was discussed. However, on the basis of IgG staining (figure 3), IgG4-related hypophysitis could not be diagnosed.

Postoperatively, the headache declined and remained remitted at the 6-month follow-up. Initially after surgery, the patient necessitated hydrocortisone replacement therapy (15 mg hydrocortisone/day) as well as 0.1 μ g desmopressin per day. The corticotroph hormone axis recovered within 6 months after surgery as did the gonadotroph hormone axis, so that the patient has regular menstrual cycles again after a 2 year-long disruption. Posterior pituitary function did not recover.

Figure 3 Histopathologic findings of hypophysis biopsy



(A) Hematoxylin and eosin stain: black arrows mark plasma cells. The brightening cytoplasm represents Russell bodies as a sign for antibody production. The green arrow marks fibrosis. (B) Hematoxylin and eosin stain: black arrows mark multinucleated giant cells; yellow arrows mark plasma cells; and green arrows mark eosinophils. (C) Biopsy revealed groups of plasma cells (CD138) and (D) IgG4-positive cells in this region. The number of IgG4-positive cells elevated up to >10 /HPF (high-power field). In (E) IgG immunostaining and (F) IgG4 immunostaining, an IgG4+/IgG+ plasma cell ratio lower than 40% was observed.

DISCUSSION Here, we describe TAC and Horner syndrome caused by a granulomatous hypophysitis in association with an elevated number of IgG4-positive plasma cells. IgG4+/IgG- ratio is low, and IgG4-positive plasma cell invasion can be seen as nonspecific. Therefore, this case does not satisfy the criteria for IgG4-related disease. Hypophysitis is a very rare neuroendocrine disease with many subtypes, some of which have only been described recently. Its early diagnosis is challenging because symptoms are often unspecific and standard cerebral MRI often lacks high-resolution imaging of the sellar region and thereby is not sensitive enough to capture subtle pituitary pathologies. Investigation of antipituitary autoantibodies does not have sufficient sensitivity and specificity for general use in diagnosis.¹ In our case, TAC was the first sign of hypophysitis and developed before clear-cut endocrine abnormalities. Horner syndrome and central suppression of the thyroid axis over time lead to reevaluation of the initial head MRI and were crucial for diagnosis. Resolution of Horner syndrome after anti-inflammatory therapy and resolution of headache after resection of the hypophysis are in accordance with an inflammatory pituitary process and confirmed the secondary origin of TAC.⁵

Underlying pathologic mechanisms of TAC related to pituitary pathology remain unclear. TAC has been described before to be associated with pituitary adenomas.⁶ Cavernous sinus invasion and mechanic dural stretch due to a pituitary mass have been postulated as potential pathomechanisms of secondary headache related to pituitary pathology in the past.⁷ The only previously reported case of cluster headache due to granulomatous hypophysitis has been associated with a large pituitary lesion with suprasellar extension and consecutive bitemporal hemianopsia.⁴ Also, small non-invasive tumors of the pituitary as well as neuroendocrinologic abnormalities itself have been described to cause secondary TAC.^{6,8,9} By contrast, our patient developed TAC and Horner syndrome due to an inflammatory process, not due to an enlargement of the hypophysis. The role of neuroinflammation related to different types of primary headache such as migraine or cluster headache has been described extensively.⁵ Moreover, this case shows that an initial recovery of headache under symptomatic therapy does not exclude a secondary headache.

To our knowledge, hypophysitis and TAC in combination with Horner syndrome have not yet been described before. The presented case shows that patients with a history of autoimmune disease (here AIP-II) and newly occurring TAC should be thoroughly searched for pituitary pathology.

How a hypophysitis causes Horner syndrome is unclear. A potential explanation is the anatomical

neighborhood between the pituitary gland on the one side and the sympathetic root, sympathetic fibers of the trigeminal nerve, hypothalamic structures, and the dorsal longitudinal fasciculus as well as the medial forebrain bundle on the other side.¹⁰ Both tracks contain fibers of the central autonomic nervous system. However, in this case, no relevant enlargement of the hypophysis was shown. Therefore, the above-mentioned explanations about the anatomical proximity of the involved structures do not explain the patients' symptoms. Hence, we suggest that autoimmune inflammation causes TAC and Horner syndrome. Our case shows that not only tumors but also autoimmune inflammation could cause disorders in these regions.⁵ Last, neuronal antibodies which target structures of the autonomic nervous system and the pituitary gland may cause Horner syndrome and TAC.

We present a case of granulomatous hypophysitis in association with TAC and Horner syndrome and establish a new differential diagnosis of Horner syndrome. Inflammatory pituitary diseases must be taken into account in case of atypical and refractory TAC, especially in patients with a history of autoimmune diseases. Repeated MRIs and appropriate endocrine tests may be needed to verify the diagnosis.

AUTHOR CONTRIBUTIONS

Jeremias Motte: data collection and drafting and revising the manuscript. Ilonka Kreitschmann-Andermahr: data collection and critical comments during manuscript revision. Anna Lena Fisse: drafting and revising the manuscript and critical comments during manuscript revision. Christian Börnke, Christoph Schroeder, and Kalliopi Pitarokoili: data collection and critical comments during manuscript revision. Oliver Müller: data collection. Carsten Lukas, Johannes van de Nes, and Rolf Buslei: data collection and critical comments during manuscript revision. Ralf Gold: critical comments during manuscript revision. Ilya Ayzenberg: data collection, drafting and revising the manuscript, and critical comments during manuscript revision.

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