Case Report: Isolated Pauci-immune Vasculitis of the Pituitary Gland Revealed by Stereotactic Biopsy

One Sentence Summary: The diagnosis of a pauci-immune vasculitis of the pituitary without systemic disease was established by stereotactic biopsy in a 36-year-old man.

Authors

R. Roelz 1, 2, D. Erny 3, M. J. Shah 1, K. Egger 4, J. Thiel 5, J. Seufert 6, K. Laubner 6, P. Reinacher 2

Affiliations

Affiliation addresses are listed at the end of the article

Case Report

A 36-year-old man was admitted to our hospital with polyuria and polydipsia, mild headaches, dizziness, fatigue and general weakness since 4 weeks. There were no other specific symptoms reported by the patient. His medical history did not reveal any previous diseases or disorders. Physical and neurological examinations were adequate. The polyuria and polydipsia in combination with low urine osmolality (102 mosmol/kg) were highly suggestive of diabetes insipidus (DI). Therefore, a water restriction test was performed. It was terminated after 12 h due to urine output of 5 l and 7% loss of body weight. With water deprivation, diuresis and low urine osmolality persisted (105 mosmol/kg at baseline and 214 mosmol/kg at termination) and serum sodium levels rose from 145 mmol/l to 154 mmol/l. Intranasal application of desmopressin 10 µg normalized serum sodium as well as hourly urine output, urine osmolality rose to 518 mosmol/kg confirming the diagnosis of central DI. Urine routine tests and urinary sediment analysis did not show abnormalities. A diabetes mellitus type 2 was ruled out.

Assessment of his anterior pituitary function showed baseline 09:00 cortisol of 286 nmol/l and adrenocorticotropic of 16.4 pg/ml (RR: 7.2–63.3 pg/ml). An ACTH-test with Stimulation with 250 µg tetracosactrin demonstrated an increase in serum cortisol to 518 mosmol/kg confirming the diagnosis of central DI. Urine routine tests and urinary sediment analysis did not show abnormalities. A diabetes mellitus type 2 was ruled out.

Key words

- vasculitis
- pituitary
- GPA

Abstract

Purpose: To demonstrate a case of isolated pauci-immune vasculitis of the pituitary gland in which the diagnosis was attained by stereotactic biopsy.

Methods: We report a 36-year-old man who presented with diabetes insipidus and secondary hypogonadism. Cranial MRI revealed an enhancing lesion of the pituitary stalk. A histological sample was obtained by stereotactic biopsy and pathological work-up provided the diagnosis of isolated pauci-immune vasculitis. No further organ manifestations or serologic signs of systemic vasculitis were identified. There was no response to immunosuppressive therapy and the patient refused treatment with Rituximab.

Conclusions: Vasculitis of the pituitary gland is a rare condition. Less than 50 cases have been described to date in patients with granulomatosis with polyangiitis (GPA, or Wegener’s granulomatosis) and few case reports exist on pituitary involvement in other systemic vasculitis like Behcet’s disease and Cogan’s syndrome [1–9]. Pituitary involvement in GPA predominantly affects the posterior pituitary gland resulting in central diabetes insipidus (DI) but global or partial anterior pituitary dysfunction and compression of the optic chiasm has also been described (10). Relapse and permanent residual pituitary insufficiency is common despite immunosuppressive therapy [7]. Vasculitis of the pituitary gland without manifestation in other organs has been described in few patients and diagnosis of GPA was attained by the presence of proteinase-3 specific ANCA and/or transsphenoidal biopsy in these cases [10–12]. The case presented here demonstrates that pauci-immune vasculitis of the pituitary can occur in the absence of systemic disease. The diagnosis can be made by stereotactic biopsy but therapy remains a challenge.
10.7 (RR: 10.6–22.7 pmol/l) was documented. Triiodothyronine (T3) was low at 3.11 pmol/l (RR: 3.4–6.8 pmol/l). Regular thyrotropic function was confirmed by a TRH (thyrotropin releasing hormone) test: Intravenous administration of 200µg TRH increased the baseline TSH from 1.44µU/ml to 7.09µU/ml after 30min. The morning testosterone level was low in repeated measurements (6.98–8.13 nmol/l, RR: 8.64–29.0 nmol/l) and partial insufficiency of the gonadotropic axis was proven by a GnRH-test (gonadotropin-releasing hormone). 100µg of intravenous GnRH prompted an adequate increase of luteinizing hormone (LH) from 3.5 to 11.4µU/ml (RR: 1.7–8.6µU/ml) after 30 min. The increment of testosterone (6.17–6.01 nmol/l, RR: 8.64–29.0 nmol/l) and follicle stimulating hormone (FSH) (1.6–2.2 mIU/ml, RR: 1.5–12.4 mIU/ml) after 30 min was low. Substitution of testosterone 25 mg daily was initiated. Prolactin was within normal range with 286µIU/ml (RR: 86–324µIU/ml), IGF-1 was also in normal range with 163 ng/ml (RR 109–284 ng/ml).

Serologic testing for antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA) antibodies, anti-phospholipid antibodies, myeloperoxidase- and proteinase 3 specific anti-neutrophil cytoplasmic antibodies (ANCA) was negative. Complement components C3, C4, and complement split product C3d were within normal range. Total hemolytic complement activity measured by CH50 was within normal limits. A high resolution computed tomography of the chest showed no abnormalities. Thus, a diagnosis of a systemic vasculitis, especially GPA (Wegener's granulomatosis) in which pituitary involvement has been described before, was unlikely. Analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture showed a cell count of 2 per µl with 90% lymphocytes, 10% monocytes and an elevated CD4/CD8 ratio of 5.3. Protein (630 mg/l) and lactate (1.36 mmol/l) levels were marginally higher than normal. There were no signs of local synthesis of immunoglobulins. The patients' serum showed normal Interleukin-2 receptor (266 U/ml), neopterin (5.6 nmol/l) and angiotensin-converting enzyme (28.7 U/l) concentrations making a diagnosis of neuroarcsoidosis improbable.

A cranial MRI revealed a single Gadolinium-enhancing nodule of 8 × 6 × 7 mm at the pituitary stalk (Fig. 1). No abnormalities of the parasellar sinuses were present. A stereotactic biopsy via a Leksell stereotaxy system and a 2.1 mm side-cutting biopsy needle. Hematoxylin-eosin stained formalin-fixed and paraffin-embedded sections of the stereotactic biopsy material showed dense perivascular as well as intraparenchymal mononuclear infiltrates (Fig. 2a, b). These infiltrates were embedded in a loose glial matrix exhibiting distinct astrogliosis as seen in the GFAP stain (Fig. 2c). The infiltrates themselves contained mainly mature lymphocytes, mostly with scarce cytoplasm and round, hyperchromatic nuclei, exhibiting CD3 and CD4 immunoreactivity (Fig. 2d, e) and several CD20-positive B cells (Fig. 2f). Only single CD8-positive cells could be detected within the infiltrates (Fig. 2g). Few plasma cells reacting positive in the CD138 immunohistochemical staining as well as immature B cells staining positive for CD79a were observed. Several CD68-positive macrophages were present. Staining for components of the complement system (C1q, C3c, C4d, C5b-9), IgG and IgG4 subclass were negative (not shown). The small blood vessel walls were fragmented, a characteristic hallmark of vasculitis, as seen clearly in the Tiber Pap Silver staining (Fig. 2h). Cloudy myelin loss (Fig. 2i) as well as axonal damage could be detected in the myelin basic protein (MBP) and Bielschowsky silver staining, respectively. Mitotic figures were absent and MIB1 staining (against the Ki-67 antigen), in which only few hematopoietic cells were marked positively, confirmed low proliferative activity. Special stains for the protozoan Toxoplasma gondii and various viruses (i.e., EBV, CMV, HSV1 and HSV2) were negative in the available specimens. Pituitary gland tissue was not detectable in the stereotactic biopsy material.

In summary, the histomorphological as well as immunohistochemical findings allowed for the diagnosis of vasculitis accompanied by secondary myelin loss and axonal damage. There was no evidence of a malignant neoplastic proliferative process. A treatment with methylprednisolone and azathioprine (AZA) was initiated and AZA was gradually increased to a daily dose of 150mg per day. MRI follow-up 10 weeks after AZA had been started showed no change of the lesion at the pituitary stalk. As we were not sure whether AZA was given long enough to reach its effect methylprednisolone dose was increased to 1 mg/kg for one week and then tapered within 5 weeks to a maintenance dose of 5 mg/d. However, MRI follow-up 6 and 8 months after diagnosis showed no response. We advocated a change of the therapeutic regimen to Rituximab but the patient refused further treatment other than hormone replacement. Diabetes insipidus and secondary hypogonadism persisted, but the patient did well under hormone replacement therapy with testosterone and desmopressin.

Discussion

Pituitary involvement in systemic vasculitis is extremely rare and most cases have been described in GPA [3–5, 7, 10, 13, 14]. Predominantly the posterior pituitary is affected causing central DI but partial or total anterior pituitary dysfunction can be present. Although the pituitary can be the first organ affected by GPA and diabetes insipidus may be the presenting symptom, systemic involvement was present or ensued in all cases of pituitary vasculitis reported to date [7, 15]. The patient presented here is, to the best of our knowledge, the first reported case of a vasculitis of the pituitary without systemic disease. Lack of immune-complex deposition (“pauci-immune”) is typical for the ANCA-associated vasculitides like GPA or MPA. As in the patient we report a pauci-immune vasculitis was diagnosed on histologic examination, we suspect a localized form of GPA or MPA in the patient. The patient was ANCA negative, but localized disease stages of GPA and MPA often lack ANCA in peripheral blood. The differential diagnoses for pituitary gland lesions are broad. Pituitary gland lesions can take both an expansive and/or invasive course. As destruction of the surrounding tissue...
rapidly leads to severe neurological deficits (vision loss, anterior pituitary insufficiency) initiation of the correct treatment is of outmost importance. We demonstrate here that it is feasible to establish the diagnosis of an isolated vasculitis of the pituitary stalk by stereotactic biopsy. The patient was started on a combined immunosuppressive treatment with azathioprine and glucocorticoids. However, follow-up MRI 6 and 8 months after diagnosis showed no response. Kapoor et al. recently reported good remission rates of DI and poor remission rates for anterior pituitary function in their series of 8 patients. Interestingly, this was independent from morphological response of the pituitary lesions on MRI [10]. In line with most published cases, our patient did not regain pituitary function as DI and secondary hypogonadism persisted [7]. Unfortunately, the patient is refusing a therapy with the B-cell depleting monoclonal antibody Rituximab (RTX). RTX has been proven to be effective in ANCA-associated vasculitis in a randomized, placebo-controlled trial and was effective in the treatment of several patients with pituitary involvement of GPA that did not respond to cyclophosphamide [10,13,14].

**Conclusion**

Vasculitis of the pituitary gland causing pituitary insufficiency was previously reported as a rare manifestation of systemic vasculitis, mainly in GPA. Serologic markers and the presence of further organ involvement can help to establish the diagnosis in systemic vasculitis. Unfortunately, diagnosing a limited, localized variant of vasculitides remains extremely challenging. The case reported here demonstrates that isolated vasculitis of the pituitary can occur in the absence of systemic disease. In this setting, stereotactic biopsy can pave the way to diagnosis and help to timely initiate therapy. Azathioprine and steroids did not induce remission in our patient. We strongly suggest a therapy with Rituximab.

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Affiliations
1 Department of Neurosurgery, University Medical Center Freiburg, Freiburg, Germany
2 Department of Stereotactic and Functional Neurosurgery, University Medical Center Freiburg, Freiburg, Germany
3 Department of Neuroradiology, University Medical Center Freiburg, Freiburg, Germany
4 Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Germany
5 Department of Endocrinology and Diabetology, Department of Internal Medicine II, University Medical Center Freiburg, Freiburg, Germany

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