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Case Report

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Occlusion of the cavernosal portion of the internal carotid artery, secondary to IgG4 hypophysitis

Abstract

Context: The pituitary gland involvement secondary to IgG4-RD is a rare entity, in addition, no reports have been identified in the literature of occlusion of the cavernous portion of the internal carotid artery, due to extrinsic compression.

Case description: We present a female patient of 54 years with panhypopituitarism, imaging findings highly suggestive of IgG4 hypophysitis, with elevated serum and CSF IgG4 levels and histopathological findings demonstrating dense fibroconnective tissue with hypereosinophilic sclerosis, these findings consistent with associated IgG4-related hypophysitis, as well as atypical sinus involvement cavernous and occlusion of the left carotid by extension of the inflammatory process, with good collateral circulation.

Conclusion: The patient was treated with steroids and Rituximab, with a decrease in serum IgG4 values and clinical improvement.

Keywords: hypophysitis, immunoglobulin G4-related disease, constriction pathologic

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Introduction

IgG4-related disease (IgG4-RD) is a multiorgan inflammatory disorder characterized by elevated serum IgG4 levels and massive lesions with storiform fibrosis and infiltration of IgG4-positive plasma cells. Organs typically affected include the pancreas, lacrimal glands, salivary gland, thyroid, lungs, skin, lymph nodes, kidneys, aorta, and retroperitoneum; the pituitary gland can also be affected.[1,2] The incidence of IgG4-RD was estimated at 0.28 to 1.08/100,000 patients in Japan,[3] however a substantial underestimation of the true prevalence of the disease is possible. The increasing recognition of this entity and the development of worldwide accepted criteria for IgG4-RD will allow for more precise epidemiological studies. Pituitary gland involvement has been reported to be rare, accounting for only 1.5% of systemic DR-IgG4 cases.[4] We present a 54-year-old female patient with IgG4-related hypophysitis associated with hypopituitarism, with an atypical involvement of the cavernous sinus and occlusion of the left carotid by extension of the inflammatory process.

Clinical case

54-year-old female patient who consulted in 2015 due to hypodynamia, presyncopal episodes and bilateral hearing loss secondary to chronic otomastoiditis, in addition, a 10-month history of galactorrhea, polyuria and polydipsia. Pituitary function studies were requested with an elevated prolactin of 116 ug/ml and a biochemical pattern of central diabetes insipidus, central hypothyroidism, and central hypogonadism without compromising the adrenal axis.

With these findings, a magnetic resonance imaging (MRI) of the sella turcica was requested, which reported diffuse enlargement of the pituitary gland (cephalocaudal diameter of 12mm), pars intermedia cyst, without evidence of hyperintensity in the neurohypophysis. Hypopituitarism was diagnosed and treatment was started with hormone replacement with levothyroxine and desmopressin, in addition to treatment with a dopamine agonist for hyperprolactinemia.

In 2017 he presented symptoms of general malaise, hypodynamia, intense headache, deterioration of visual and auditory acuity, dysgeusia and muscular fatigue, for which neuroimaging control was requested with pachymeningeal enhancement, not identified in previous studies, which compromised the sphenoid plane, floor of the left middle cranial fossa, Meckel's cavum and left foramen ovale; findings highly suggestive of IgG4-RD (Figure 1).

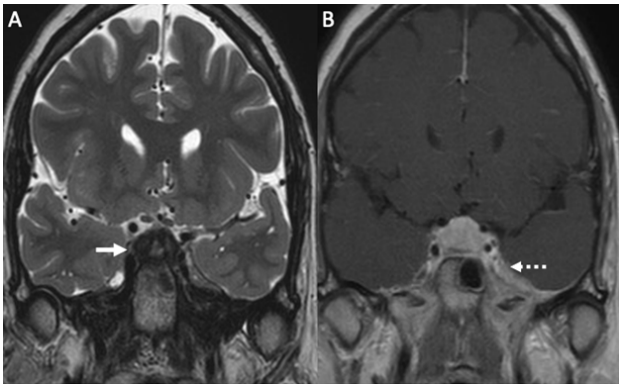

Figure 1 A. Coronal T2 sequence, decreased signal intensity of the gland (white arrow) B. Sagittal T1 sequence, after contrast administration: pituitary enlargement, with diffuse enhancement. Thickening and enhancement of the sphenoid plane, the floor of the left middle cranial fossa, Meckel's cavum and the foramen ovale on the left side (dashed white arrow).

He was hospitalized for extension studies, a serum IgG4 elevation of 1.89 g/L was documented (reference values 0.039-0.864 g/L). Additionally, infectious, granulomatous or tumor diseases were ruled out and treatment with methylprednisolone boluses was started with improvement of signs and symptoms. He was discharged with prednisolone, levothyroxine, and desmopressin.

In 2018 he presented a relapse of his symptoms, for which a lumbar puncture was performed with elevated IgG4 in cerebrospinal

fluid, a transsphenoidal biopsy of the pituitary was requested, the result of which reported a pituitary parenchyma surrounded by dense fibroconnective tissue with hypereosinophilic sclerosis in a laminated pattern and inflammatory cells in the interstice. These histopathological findings associated with elevated serum IgG4 levels were consistent with IgG4-RD. Treatment with methylprednisolone and cyclophosphamide was started with partial clinical improvement (Figure 2). At the end of 2018, he presented again with intense headache, for which an MRI of the sella turcica was performed, which showed extension of the inflammatory process to the left cavernous sinus, to the trigeminal cistern and invasion through the foramen ovale with extensive pachymeningeal enhancement in the left temporal base. Magnetic resonance angiography revealed occlusion of the left internal carotid artery (Figure 3), other associated vasculitis was ruled out, and treatment with Rituximab was started.

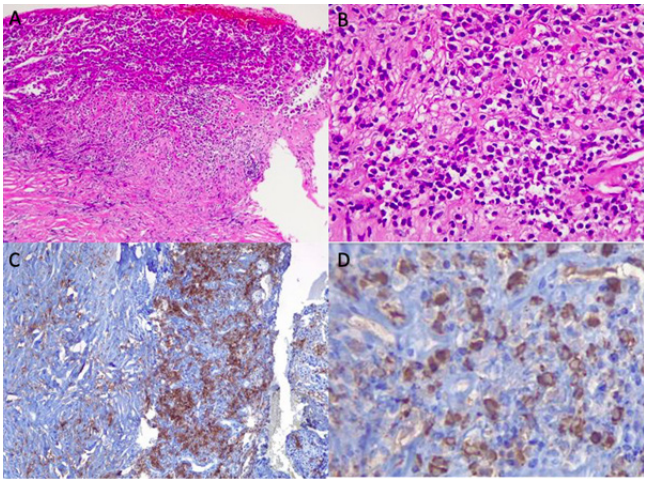

Figure 2 A H&E 50x B (H&E) 100x Pituitary parenchyma, surrounded by dense connective tissue, with a sclerosing appearance. Inflammatory cells in the interstitium. Hypereosinophilic sclerosis in laminated pattern. C. Ig4 50x staining D. Ig4 100x staining Marked reactivity in large numbers of plasma cells. (H&E): haematoxylin and eosin.

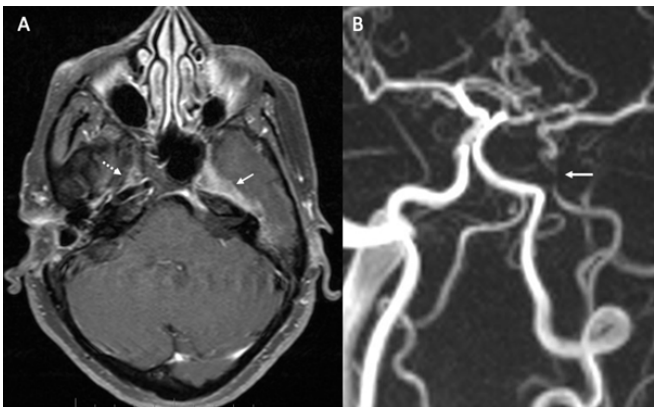

Figure 3 A,T1 axial sequence after contrast administration: Stenosis of the left internal carotid artery (solid white arrow), compared with the contralateral carotid artery (dashed white arrow) B. MIP reconstruction of angioresonance: Stenosis of the left internal carotid artery. MIP, maximum intensity projection.

In 2019, the control MRI showed persistence of the occlusion of the left internal carotid, in the brain parenchyma, no ischemic or demyelinating lesions were demonstrated, which suggested good collateral circulation through the anterior communicating artery (Figure 4). The patient after the start of Rituximab is stable, asymptomatic, with IgG4 values in May 2021 at 0.77 g/L.

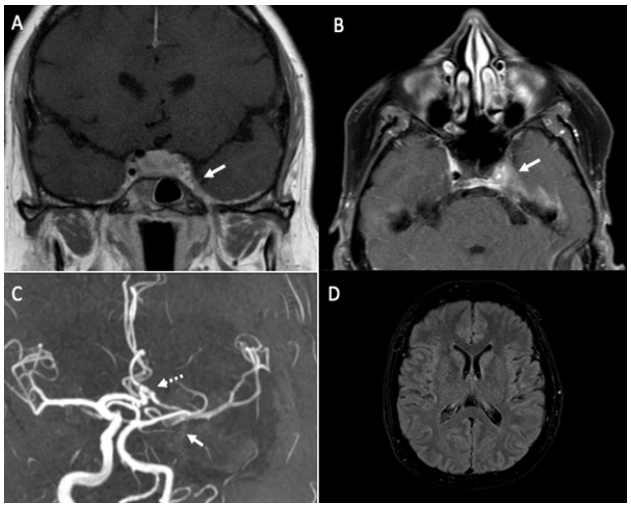

Figure 4 A, T1 coronal sequence, after contrast administration B, T1 axial sequence, after contrast administration. Progression of involvement and complete stenosis of the left internal carotid artery (solid white arrow), C, MIP Reconstruction of Angioresonance: complete stenosis of the left internal carotid artery (solid white arrow), with contribution through the anterior communicator in the polygon (dashed white arrow). D, axial FLAIR sequence, there are not ischemic lesions, due to collateral circulation. MIP, maximum intensity projection; FLAIR, fluid –attenuated inversion recovery.

Discussion

IgG4-related (IgG4-RH) hypophysitis, which affects the hypothalamus and pituitary, accounts for 1.3% of primary hypophysitis. The incidence ratio of men to women is 3.2: 1 and the average age of onset is 66.3±11.5 years.[5] The main pathological features include the infiltration of positive IgG4 lymphocytes in the hypothalamic-pituitary area, which occurs mainly with central diabetes insipidus. A study showed manifestations such as hypopituitarism in 26% and panhypopituitarism in 52.4% of the patients.[6]

The gold standard for the diagnosis of IgG4-RH is pituitary histopathology,[7] however the findings in the pituitary MRI and the histopathological involvement of other organs may suggest the diagnosis. In our case, the radiological findings on MRI led to suspicion and finally to confirm this entity.

Recent reports have shown that IgG4-RH could be detected in 30% of cases of hypophysitis and in 4% of all cases of hypopituitarism and/or diabetes insipidus (DI).[8] However, the pathogenesis of IgG4-RH remains unclear due to the limited number of case reports.[9]

Depending on whether the clinical symptoms and MR images involve the anterior lobe or the pituitary stalk and posterior lobe or both, hypophysitis has also been classified as adenohypophysitis, infundibulo-neurohypophysitis, and panhypophysitis. Adenohypophysitis tends to develop hypopituitarism and pituitary mass, whereas clinical presentations of infundibulo-neurohypophysitis often include DI accompanied by inflammation of the pituitary stalk. However, there are reports in the literature that IgG4-RH can affect both adenohypophysitis and the infundibulum-neurohypophysitis structure.[8,9] In our case, radiologically there was no infundibular involvement, however hyperintensity of the neurohypophysis was not evidenced and both hypopituitarism and DI coexisted.

IgG4-RD has been gaining more and more importance in medicine and medical literature, positioning itself as "the new great simulator". This is how cases of IgG4-RD simulating multiple meningiomas, cholangiocarcinoma and pancreatic cancer have been published.[10]

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In our case, in addition to hypophysitis, there was evidence of extension of the inflammatory process to the left cavernous sinus, to the trigeminal cistern and invasion through the foramen ovale with extensive pachymengeal enhancement in the left temporal base. At angio-MRI, occlusion of the left carotid was found.

Cavernous sinus involvement secondary to multiple diseases such as vascular, neoplastic, infectious and inflammatory pathologies has been described, within the latter group are sarcoidosis, histiocytosis, Tolosa-Hunt syndrome and IgG4-RD. It is difficult to differentiate the nature of the lesion solely by neuroimaging,[11] however, in IgG4-RD there is evidence of a marked hypointense signal in T2 related to fibrosis, similar to granulomatosis with polyangiitis. Useful clues for making the diagnosis include involvement of other structures of the head and neck, including the salivary or lacrimal glands, thyroiditis, orbital inflammatory pseudotumor, pachymeningitis, and pituitary hypophysitis, the latter two found in our patient.[12]

Vascular involvement in the context of IgG4-RD is being increasingly recognized and the majority of cases belong to patients with aortitis and/or periaortitis with or without aneurysm formation. However, it is now clear that other vessels such as the iliac, coronary, and carotid arteries can also be affected and are often underdiagnosed.[13]

The involvement of the carotid arteries by IgG4-RD has already been reported in the literature, there are reports of involvement by vasculitis with aneurysmal involvement and different degrees of stenosis up to total occlusion of the internal carotid artery.[14]

Vascular involvement by IgG4 can be primary or secondary. Primary vasculitis predisposes to aneurysm formation and, occasionally, to dissection or perforation. In secondary school, the related vascular disease is more likely to cause arterial stenosis. The distinction between primary vasculitis and secondary vascular involvement is important for predicting outcomes and guiding optimal therapy. In a series of cases, the histopathology of large vessel vasculitis in IgG4-RD was described in which it was evidenced that the cellular infiltrate of the vasculitis predominantly affects the adventitia, with less involvement of the media in contrast to the inflammatory infiltrate that it focuses on the average in other forms of vasculitis.[15] Secondary vascular involvement occurs due to the compressive effect of the swollen lesions for which IgG4-RD is known. Perivascular soft tissue abnormalities are minimal in primary vasculitis, and inflammation is centered in the vessel wall itself. In contrast, the predominant features of secondary vascular disease are enhancement and thickening of the perivascular soft tissues with avidity for fluorodeoxyglucose (FDG), but inflammation within the vessel wall itself appears to be minimal.[15]

There are also clinical differences between these two categories of vascular disease in IgG4-RD. Patients with primary vasculitis have greater elevations in total serum IgG and a trend toward greater elevations in IgG1, IgG4, and C-reactive protein. These patients are also much more likely to have signs or symptoms directly attributable to vascular involvement compared to those with secondary vascular disease. Only 13% of the patients with secondary vascular compromise presented signs or symptoms directly attributed to their vascular compromise, a finding compatible with other reports.[16,17]

PET-CT with the angiography component that includes the noncontrast, postcontrast, and delayed arterial phases is the most appropriate imaging study to evaluate the walls of the great vessels for evidence of enhancement, thickening, aneurysm, or uptake of FDG. This imaging modality is especially important in distinguishing true vessel wall involvement (primary vasculitis) from adjacent inflammatory tissue (secondary vascular involvement).[15]

In our patient, it was considered that the unilateral occlusive involvement of the internal carotid is due to vascular involvement secondary to the extension of the perivascular inflammatory process and there is no primary vasculitis, due to the symptoms and findings found on MRI.

In addition, it has been shown that many of the lesions found in patients with IgG4-RD that were previously thought not related to the disease, commonly show characteristics that include inflammation of the affected organ such as a tumor with lymphoplasmacytic infiltrate, enriched with plasma cells with grade fibrosis variable, with a storiform pattern characteristic of IgG4-RD.[18,19]

The natural history of the disease is uncertain. In our case, the patient presented an initial response to glucocorticoid therapy but with a subsequent relapse of the disease requiring the start of Rituximab. Steroid therapy is the first treatment option for IgG4-RH, in one study, more than 90% of patients had reduced inflammation of pituitary lesions after therapy.[6] In other publications, more than 60% of patients did not improve pituitary function after therapy (8,20). IgG4-RH has been shown to relapse during steroid tapering, but in patients without relapse, the prognosis of pituitary function after treatment with this drug has not been clarified.[1]

In a study published in 2017, it is evidenced that glucocorticoid therapy can improve anterior pituitary function, but does not have an effect on posterior pituitary function and does not improve DI.[21] Our patient has improved since the start of Rituximab. In a case report, he demonstrated how a patient with IgG4-RH has a better response and improvement of his symptoms with the combined treatment of pulsed methylprednisolone and Rituximab.[22] It was observed in a case series of three women that Rituximab treatment resulted in sustained remission and complete recovery of anterior pituitary function with reduction in the size of the pituitary gland in two patients who started treatment early; In patient three who started Rituximab late, symptom improvement was demonstrated, but pituitary hypofunction and gland enlargement persisted, thus emphasizing the importance of early therapeutic intervention to avoid irreversible changes.[23]

Conclusion

The forms of presentation of IgG4-RD are innumerable but it is necessary to make an early diagnosis to avoid unnecessary surgeries and obtain a better therapeutic response with the least development of residual fibrosis. IgG4-RH is rare and the key to its diagnosis is histopathology, however, in our case, radiological findings were essential not only to suspect and diagnose this entity but also to detect complications and document the response to therapy. The involvement of the internal carotid has already been reported previously in the literature, however, as far as we know, this is the first manifestation of IgG4-RH with complete unilateral occlusion of the internal carotid secondary to extension of the inflammatory process to the cavernous sinus and not secondary to vasculitis.

Acknowledgments

None.

Conflicts of interest

The authors have nothing to declare.

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