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ORIGINAL COMMUNICATION

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Idiopathic inflammatory pseudotumor of the orbit and Tolosa-Hunt Syndrome – are they the same disease?

Abstract Unilateral periorbital pain, cranial nerve palsies and a dramatic response to corticosteroid therapy are the hallmarks of clinical presentation in Tolosa-Hunt-Syndrome (THS) and Idiopathic Pseudotumor of the Orbit (IIPO). Both are unspecific chronic granulomatous diseases of unknown origin, sharing clinical as well as paraclinical characteristics. We observed two patients suffering from acute granulomatous IIPO, who also fulfilled the criteria of THS. Patient 1 developed leftsided infiltration of the medial ocular muscle with periorbital pain and cranial nerve palsy. After an initial response to corticosteroid therapy, contralateral relapse occurred with a THS-like infiltration of the sinus cavernosus and narrowing of the intracavernous internal carotid artery. Granulomatous infiltration of the right sinus cavernosus with secondary involvement of the ipsilateral nervus opticus and a slight exophthalmos was seen in Case 2. According to the literature, MRI and CT show identical signal intensity with different localisation: IIPO preferentially intra- and THS retroorbital. Apart from neuroradiological findings, almost similar histopathology and clinical presentation makes it difficult to distinguish between these two syndromes. Similarities between these two syndromes have been discussed for more than 20 years. Our two cases show their close relationship and we suggest that both diseases belong to the same pathological process.

Key words Idiopathic Inflammatory Pseudotumor of the Orbit · Tolosa Hunt Syndrome

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Introduction

Both Idiopathic Inflammatory Pseudotumor of the Orbit (IIPO) and Tolosa-Hunt-Syndrome (THS) represent unspecific chronic granulomatous inflammatory processes of unknown origin. Unilateral periorbital pain, cranial nerve palsies (III,IV,V1/2,VI) and response to corticosteroid treatment are the hallmarks of the clinical presentation. In IIPO a mass effect of inflammatory tissue can lead to exophthalmos [16]. For the diagnosis of both syndromes, the exclusion of a malignant tumor by MRI and CT and an adequate clinical and radiological follow-up extending up to 2 years are essential [7]. For both conditions corticosteroids and immunosuppressive agents are the treatment of choice. We observed two patients suffering from acute granulomatous IIPO with secondary extension into the sinus cavernosus. Their clinical and paraclinical findings show the close relationship and the problems of distinguishing between these two syndromes.

Case 1

In July 1992 a 38-year-old male was admitted to hospital with left periorbital pain and exophthalmos. The initial CT showed a hyperdense thickening of the left musculus rectus medialis with lateral displacement of the optic nerve. In laboratory examinations no systemic inflammatory or malignant disease was found (e. g. CSF: 5/3 lymphocytic cells with normal glucose, protein and lac-

tate levels, no oligoclonal bands. Normal red and white cell counts, C-reactive protein, angiotensin converting enzyme, thyroid stimulating hormone levels and serum electrophoresis. Autoimmune antibodies ANA, ANCA, ENA, AMA negative). After starting corticosteroid treatment in a weight adapted dose of 1 mg/kg, pain resolved within a few days. Three months later visual loss on the affected side occurred. CT showed progression of the inflammation now with involvement of the nervus opticus. In cerebral MRI the left medial muscle showed an isointense signal on T1 scans with contrast enhancement. Assuming endocrine orbitopathy with myositis, orbital radiation with 10 * 1 Gy was started. Though continuing the steroid treatment, there was further worsening of visual loss and exacerbation of left periorbital pain. A few months later biopsy of the left musculus rectus medialis was performed by a transfrontal approach. The macroscopic greyish muscle showed histologically a little infiltration of granulocytes and edema, interpreted as an unspecific myositis. In September 1993 the patient reported rightsided temporal burning headache, hypo-/dysesthesia of the first trigeminal branch, ptosis, visual loss and diplopia. MRI showed a contrast enhancing lesion (T1) isointense to muscle in the right sinus cavernosus extending to the tentorium.

Cerebral angiography demonstrated severe narrowing of the intracavernous section of the internal carotid artery and of the proximal A. cerebri media. Corticosteroid treatment was replaced by a parenteral pulse therapy of 640 mg cyclophosphamide, followed by oral 150 mg/die until the maximum dose of 80 g. Until January 1998 the immunosuppressive therapy was continued with 100 mg of oral azathioprin. In a follow up MRI in 1994 the isointense parasellar contrast enhancing lesion was no longer seen. Now for 9 years the patient has shown no clinical progression.

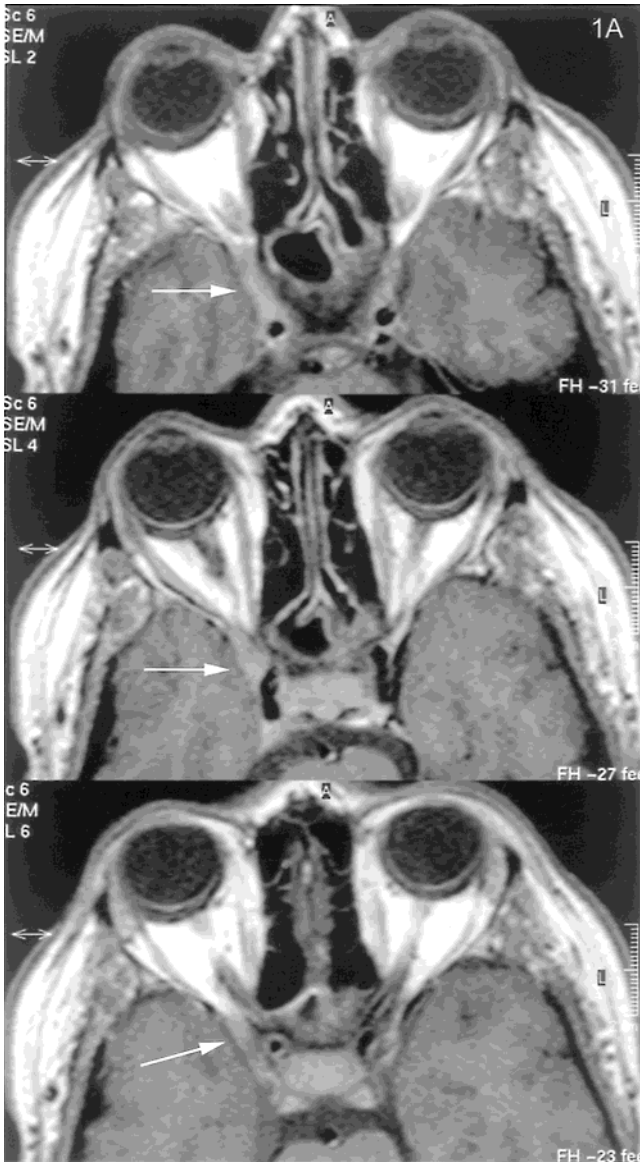


Fig. 1 A T1 weighted images of the fissura orbitalis superior and the sinus cavernosus of Case 2. Transverse unenhanced images. Soft tissue mass (→) lateral of the right optic nerve penetrating the sinus cavernosus with narrowing of the ICA.

Case 2

In March 2000 the 38-year-old female patient experienced transient diplopia over six weeks. Six months later she was admitted to our clinic with subacute rightsided periorbital pain, hypesthesia of the first and second division of the trigeminal nerve and partial palsy of the N. oculomotorius. As in Case 1 laboratory findings were in the normal range (CSF: 1/3 lymphocytic cell with normal glucose, protein and lactate levels, no oligoclonal bands. Normal R/WBC, CRP, ACE, TSH levels and serum electrophoresis. ANA, ANCA, ENA, AMA negative).

MRI revealed a contrast-enhancing process isointense (T1) to muscle spreading from the right orbital apex through the superior fissure to the sinus cavernosus (Fig. 1). Coronary CT showed no pathological intraorbital findings. Tolosa-Hunt syndrome was diagnosed and oral corticosteroid treatment started in a dose of 1 mg/kg/die. Pain resolved within 24 hours. After clinical remission over 3 months, the patient developed subacute exophthalmos, palsy of the third, fifth and sixth cranial nerve with acute visual loss. Surgical exploration of the right orbit and the optic canal was performed. Histological examination showed a granulomatous infiltrated soft tissue surrounding the optic nerve. Diagnosis of acute granulomatous IIPO was made and corticosteroid treatment replaced by oral cyclophosphamide in a dose of 100 mg/die. In July 2001 follow-up MRI demonstrated only a little inflammatory tissue and minimal focal enhancement of the optic nerve (Fig. 2).

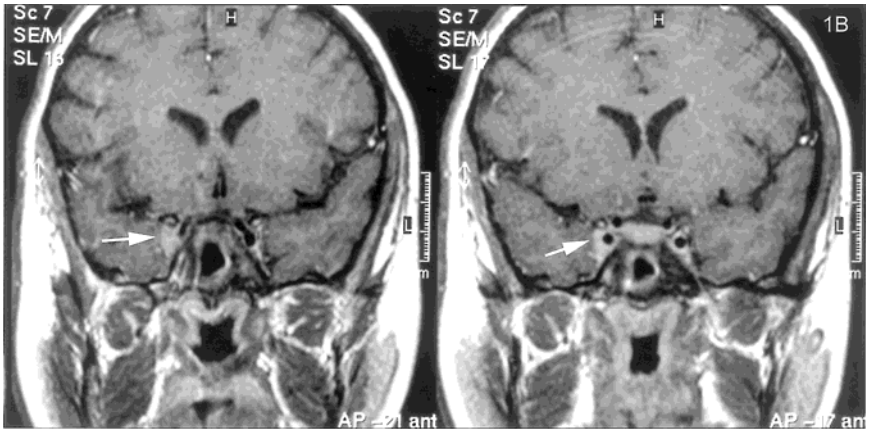
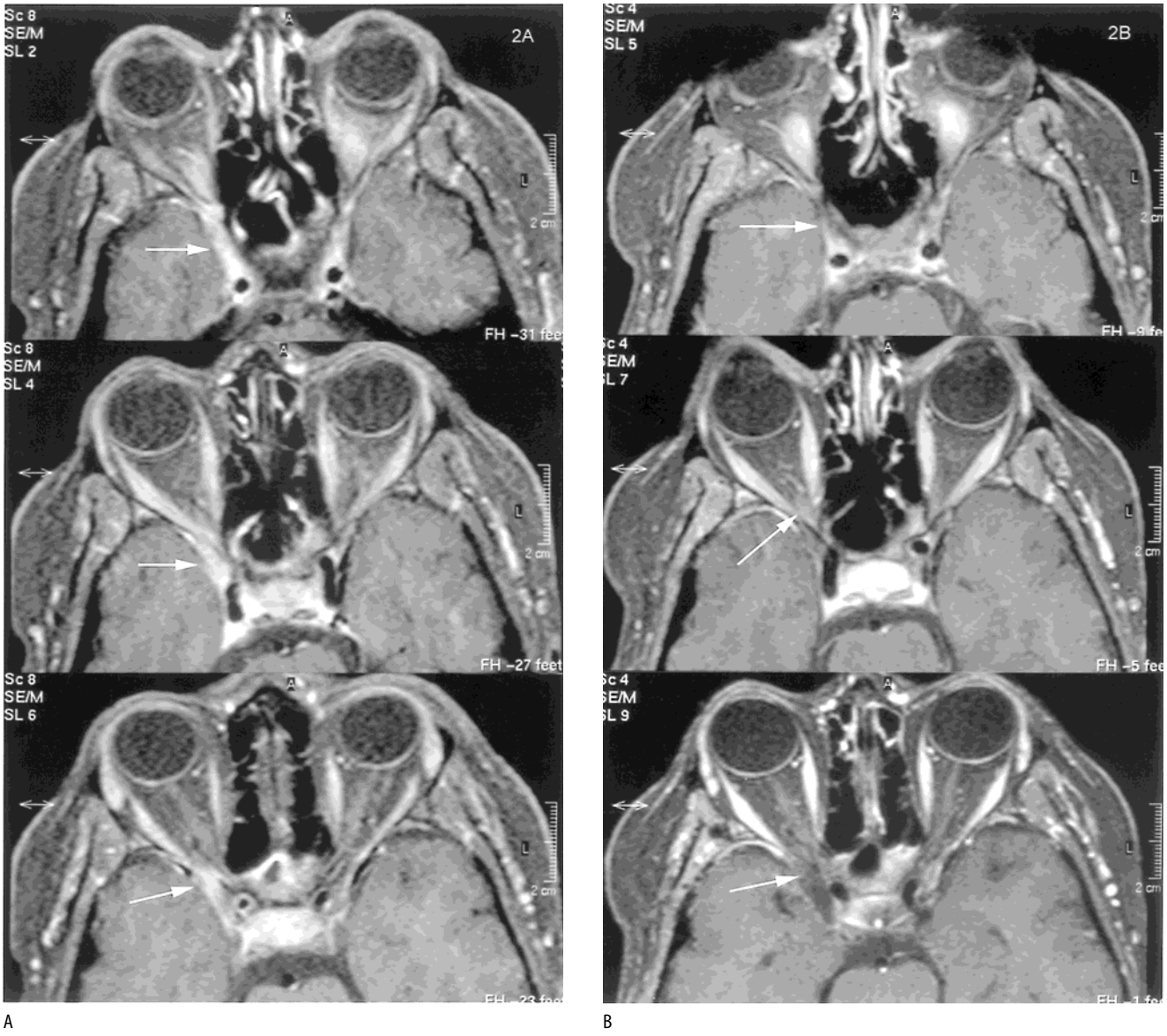


Fig. 1 B Coronary images demonstrate a slight contrast-enhancement of the lesion above (→)



A B

Fig. 2 Fat suppressed T1-weighted transverse images of Case 2. Before (**A**) and after (**B**) surgical removal of the soft tissue mass (→)

On last clinical examination in August 2001 the patient showed ongoing rightsided hypesthesia of the first and second trigeminal nerve and a slight abduction deficit of the bulbus, but no exophthalmos or visual loss.

Discussion

Clinical and histopathological features

IIPO is an intraorbital disease presenting as myositis (Case 1), dacryoadenitis, periscleritis, inflammation of the trochlear muscle, perineuritis (Case 2) or infiltration of the intraorbital fat. Intracranial expansion as in Case 1 through the superior orbital fissure is known. To date only 19 cases of extraorbital IIPO have been reported [2]. Retro-orbital THS is characterised by inflammatory infiltration of the sinus cavernosus and/or the superior orbital fissure [7]. In our two cases of IIPO involvement of the sinus cavernosus is also shown.

Subacute/acute periorbital pain with cranial nerve palsies is the common clinical feature shared by these two syndromes. Owing to the intraorbital mass effect, exophthalmos is only seen in IIPO.

THS occurs bilaterally in only 5 %, whereas IIPO is usually a unilateral disease with a higher incidence of bilateral courses in childhood [16].

About 40 % of THS patients suffer from ipsi- or contralateral relapses of the disease [15]. Constantinidis et al. reported 3 out of 6 [6] and Mombaerts et al. 11 out of 21 (52 %) [12] patients with IIPO having a relapse after initial response to corticosteroid treatment. In Case 1 contralateral relapse occurred after one year. There may be recurrence even after a 10 year interval [16].

Spontaneous remission occurs in 28 % [5] of IIPO and in 85 % [15] of THS. This could be due to the different histological types in IIPO. Histological findings are of the acute granulomatous type with a polymorphous infiltrate composed of mature lymphocytes, plasma cells, macrophages, eosinophiles and polymorph nuclear leucoctyes [16]. In Case 1 and 2 biopsy specimens showed soft tissue infiltrations of the acute granulomatous type. Though histological reports of THS are rare, almost identical granulomatous infiltrations have been described [8, 11, 13].

Subacute and chronic time courses in IIPO are histologically characterised by an increasing amount of fibrovascular stroma with fixation of orbital structures. Lymphoid follicles with germinal centers may be interspersed.

Both syndromes represent an unspecific granulomatous inflammation of unknown local or systemic cause.

Radiological findings in MRI, CT and angiography

Yousem et al. [17] found in a series of 11 patients with THS similar signal intensity to orbital pseudotumor. THS appears on T1 weighted MRI as hypointense relative to fat and isointense with muscle and on T2 scans isointense with fat. As shown in our two cases, identical signal intensity is known in IIPO [16]. Both conditions show a prominent gadolinium enhancement due to the inflammatory process. In a chronic course of IIPO the contrast enhancement can decrease depending on the ongoing fibrosis. The main difference is the localisation of the inflammation: The most frequently involved intraorbital structure in IIPO is the lacrimal gland, followed by intraorbital muscles, fat and the optical nerve sheath. On the other hand THS lesions extend from the sinus cavernosus to the superior orbital fissure. One of the diagnostic criteria of THS is the convex enlargement of the sinus cavernosus [1]. These characteristics have also been described in cases of extraorbital expansion of IIPO [16]. Narrowing of the intracavernous portion of the internal carotid artery is a frequent finding in angiography of THS patients [4].

Apart from our Case 1, there is one further case report in the literature of carotid narrowing in IIPO proven by angiography [2].

All the described radiological criteria for THS such as signal intensity in MRI, localisation, enlargement of the sinus cavernosus and narrowing of the ICA can also be found in our two cases of IIPO. Occlusion of the superior ophthalmic vein in orbital phlebography has been found in THS and in IIPO [4].

The dominant role of CT in the diagnosis of THS and IIPO is the exclusion of bony eroding tumors e. g. from the surrounding sinus. CT can show intraorbital extension in IIPO, but is insensitive to intracranial expansion. There are no differences in density values of THS or IIPO [3] and a variable contrast enhancement in IIPO. In a study of 12 patients with idiopathic painful ophthalmoplegia, Goto et al. found 6 patients with a high density area in the orbit. This abnormal area was not seen on CT performed less than one month after onset of the symptoms, but some patients developed intraorbital abnormalities in follow up CT. In early stages of disease, no difference can be found between THS and IIPO on CT [9].

Response to steroids and immunomodulation

Dramatic response to corticosteroid treatment within 72 hours is one of the diagnostic criteria for THS defined by the International Headache Society 1988. A dose of 1 mg/kg over 14 days is the common regime [3]. Corticosteroid response is also seen in IIPO, especially in the acute granulomatous forms. Both of our two patients

showed a complete regression of pain within a few days. Reports of an overall effect of corticosteroids in IIPO differ from 35 % to 78 % of initial responders [5, 12]. In the chronic fibrotic or lymphocytic forms, orbital surgery or local radiation is the therapy of choice. Corresponding to other observations in IIPO [12], monotherapy with corticosteroids in Case 1 and 2 was not effective in the long term and additional other immunosuppressive drugs were needed. On initial treatment with oral cyclophosphamide followed by azathioprine, both patients show no clinical or radiological progression for 9 and 1 year(s) respectively.

Differential diagnosis

IIPO and THS share the response to corticosteroid treatment, clinical features and MRI characteristics with several other intra-/retroorbital diseases. For example it can be very difficult to differentiate between IIPO and intraorbital lymphomas: both respond to steroid therapy, both show the same MRI signal intensity and can have the same clinical presentation. Other differential diagnoses include cerebral sarcoidosis, lupus erythematodes, Wegener disease, intraorbital tumors, tuberculosis, mycosis, cranial neuropathy (e. g. mononeuritis multiplex, ophthalmoplegic migraine, aneurysm, diabetes mellitus).

Therefore in cases of intraorbital inflammation with rapidly progressive neurological deficits, with lack of steroid responsiveness or persistent abnormalities on neuroimaging studies, biopsy should be performed [10]. In THS Föderreuther [7] proposes adequate clinical and radiological follow up examinations performed for at least two years.

As one can see both syndromes can be simulated by various other disorders and so it still remains a diagnosis of exclusion.

Conclusion

IIPO and THS are two nearly related syndromes treated as distinct entities until now. Both are unspecific granulomatous infiltrations of unknown local or systemic origin. They share the same clinical features, with periorbital pain, cranial nerve palsies and (in acute IIPO forms) often dramatic response to corticosteroid therapy. MRI and CT findings show identical signal intensity with different localisation, IIPO preferentially intraorbital and THS retroorbital. Our two cases illustrate the close relationship: In Case 1 beginning with intraorbital inflammation on the one side, the contralateral relapse fulfilled the criteria of THS. In Case 2 the disease started with a THS-like inflammation followed by visual loss due to perineuritis and a slight exophthalmos as known from IIPO.

Similarities between THS and IIOP have been discussed for more than 20 years [13]. In accordance with these previous observations our two cases show that THS and IIPO are two closely related syndromes, which may belong to the same pathological process.

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