Chronic recurrent multifocal osteomyelitis presenting with Tolosa-Hunt syndrome in a 13-year-old boy

Sirs,

Tolosa Hunt syndrome (THS) is a rare disease caused by idiopathic granulomatous inflammation of the cavernous sinus or superior orbital fissure, characterised by periorbital or hemicranial pain associated with ipsilateral ophthalmoplegia and a rapid response to treatment with corticosteroids.

Its aetiology is unknown, the diagnosis of THS requires to rule out vascular, neoplastic, traumatic, infectious and other inflammatory causes, such as sarcoidosis, granulomatosis with polyangitis, giant cell arteritis (1). THS is extremely rare in children, the mean age at onset is 38-41 ± 14-16 years (2). In 2004, the International Headache Society (IHS) re-defined the diagnostic criteria of THS specifying that granuloma, demonstrated by magnetic resonance imaging (MRI) or biopsy, is required for diagnosis (3).

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder whose pathogenesis is still not well defined. Bone inflammation is frequently accompanied by inflammatory disorders of joints, skin, or intestine (4). CRMO typically involves long bone metaphyses; only three cases of CRMO involving the neurocranium have been described so far (5, 6). Rheumatic disease, infective osteomyelitis, and malignancy are the main differential diagnoses together with other autoinflammatory bone diseases such as cherubism, an autosomal dominant disorder affecting the maxilla and mandible, characterised by bilateral enlargement of the mandible and/or maxilla as bone is replaced with painless, cyst-like growths (7).

CRMO and THS have never been described in the same patient. We report the case of a young boy diagnosed with CRMO at the age of 13 years and 2 months, who presented with Tolosa-Hunt syndrome 8 months before the diagnosis of CRMO.

We report the case of a previously healthy 12-year and 6 month old boy presenting with a 9-day history of right orbito-temporal headache unresponsive to nonsteroidal anti-inflammatory drugs and right ptosis lasting for one day. His relevant medical history only included a hospitalisation for mononucleosis three months before. Physical, neurological and eye examination were unremarkable, with the exception of right ptosis. Complete blood count, electrolytes with glucose, thyroid function tests, fluorescent treponemal antibody, angiotensin-converting enzyme (ACE), antinuclear antibody (ANA), Antineutrophil cytoplasmic antibody (ANCA), Lyme titre, intracutaneous Mantoux test, bacterial cultures were negative. Erythrocyte sedimentation rate resulted moderately elevated. The brain computed tomography (CT) scan, performed without contrast agent, was normal. The brain magnetic resonance imaging (MRI) showed the presence of a mass lesion expanding the right cavernous sinus, with intense enhancement after contrast injection, suggestive for granuloma. After contrast agent administration, enhancement was observed in the above described lesion but also in the adjacent meninges, especially whose of the anterior cranial fossa (Fig. 1).

Diagnosis of Tolosa-Hunt syndrome was made and steroid therapy was started, with prompt clinical benefit. The brain MRI performed one and three months later, showed progressive resolution of inflammation. Following the steroid tapering, at the age of 13 years and 2 months, diffuse arthralgias appeared, together with right wrist swelling. Radiologic investigations documented the presence of lytic lesions in the right distal ulna, in the right femoral trochanter and in T4 and T6 vertebral bodies. Laboratory tests were unremarkable, except for increased acute phase reactants. Cultures and serological tests did not evidenced signs of infections. The patient underwent a bone marrow biopsy and bone biopsy of the right distal ulna that excluded the presence of neoplasms or infections, and he was diagnosed with CRMO. Treatment with indomethacin was started with clinical improvement up to complete normalisation of acute phase reactants.

The brain CT scan and MRI performed at disease onset were re-evaluated to research for eventual bone lesions misdiagnosed at the first evaluation. CT scan was confirmed completely negative for bone lesions, however at MRI, an abnormal contrast enhancement of the right anterior clinoid process indicated the presence of signs compatible with bone inflammation (Fig. 2). Inflammatory involvement of the cavernous sinus and the adjacent tissues, as shown in MRI images (Fig. 1), can be primitive and responsible for the contrast enhancement evidenced on the right anterior clinoid process, or it could be secondary to the phlogistic process occurring in the bone of the cranial base, as it often occurs when osteolytic lesions determine tenderness, swelling, or warmth in the tissues overlying the involved bone.

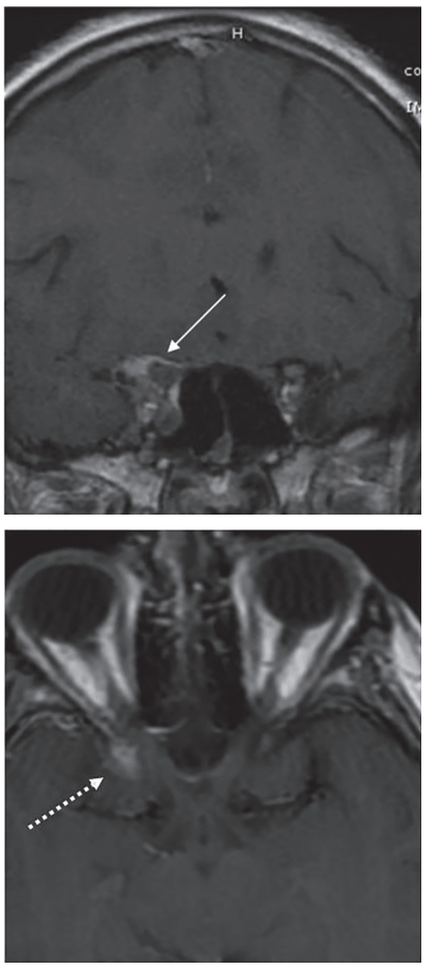

Fig. 1 - 2. TSE T1 coronal (1) and axial (2) MRI images after gadolinium document the presence of pathological tissue characterised by enhancement in correspondence of the right cavernous sinus, suggestive for granuloma. The images also show an abnormal impregnation of the dura mater covering the right cavernous sinus and the anterior cranial fossa (Fig. 1, the white arrow), as well as of the anterior clinoid (Fig. 2 , the dotted white arrow).

CRMO is an autoinflammatory disease and typically involves long bone metaphyses at any site of the skeleton; it was thought to spare the neurocranium (4). There is increasing evidence for the theory that CRMO is genetically driven, but to date no single gene variant has been linked to the onset of CRMO (4, 7). The precise pathophysiology of CRMO remains unknown. However, recent findings evidenced that an abnormal regulation of IL-1β axis may be involved in CRMO pathogenesis (8, 9). Studies performed on chronic multifocal

osteomyelitis (CMO) mouse model confirmed that IL-1β is a critical cytokine in the pathogenesis of osteomyelitis in the cmo mouse (9), and it is activated by the macromolecular NLRP3 inflammasome complex.

It has recently been reported the case of a patient diagnosed with THS, in whom genetic analyses revealed a heterozygous low-penetrance mutation (Q703K) of the cryopyrin/NLRP3 gene (10).

In our patient, the classical picture of THS preceded the full blown presentation of CRMO.

Even if the possible existence of a link in the pathophysiology of THS and CRMO is only a speculation, we underline the opportunity to consider also this rare autoinflammatory disease among the possible causes of neurological manifestations.

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