Methotrexate-induced hiccups

Sirs, A hiccup is defined as a sudden contraction of the inspiratory muscles followed by an abrupt closure of the glottis, producing the characteristic sound. Two kinds of hiccups can be distinguished: acute hiccups, benign and self-limited; and persistent hiccups, intractable, with a duration exceeding 48 h. Acute hiccups are mostly linked with oesophagogastric causes, generally distension occurring after a hearty meal, a rapid intake of drink or during endoscopia or intubation. However, a sudden change in temperature, alcohol intake or emotional factors can also set off acute hiccups. A spontaneous resolution is observed minutes after the beginning. Persistent hiccups have multiple aetiologies: generally stimulation of the nervous route due to an inflammatory, compressive, infectious or metabolic pathology [1].

Drug-induced hiccups are rare and their diagnosis is based on the elimination of other causes associated with suggestive chronological criteria. Benzodiazepines and CSs are the drugs most often mentioned [2, 3]. However, some cases have also been reported with anti-neoplastics, antibiotics, anti-psychotics, cardiovascular drugs, antidepressants and dopaminergic agonists [4]. The mechanisms responsible for this side effect are still not known. Here, we report the case of a woman who developed recurrent hiccups during oral MTX treatment for PsA.

The patient, a 26-year-old pianist, suffered from HLA-B27-positive PsA up to the age of 15 years. During her childhood, her treatment was based only on steroid therapy. However, she developed intolerance to these drugs and she herself decided to stop all drug intake. After an 8-year period without follow-up, the patient again complained of an increase in painful symptoms in her hands, back and knees that made it impossible for her to continue her job. Results of laboratory and immunological examinations were within the normal range: sedimentation rate 6 mm/h, CRP 0.4 mg/l. Her haemogram, hepatic and renal functions and phosphocalcic balance were also normal. An oral treatment of MTX at a dose of 10 mg (four 2.5 mg tablets, once a week) and folic acid (i.e. monohydrate lactose, starch corn, magnesium stearate and sodium hydroxide) are commonly used for the formulation of many tablets and are considered to be safe, the oral administration route of MTX appears to be the major factor responsible for the occurrence of the hiccups in this case. It is possible that MTX caused local gastrointestinal irritation of the mucosa, as its gastrointestinal side effects are very common, particularly after oral administration [6, 7]. An irritation could be caused by a prolonged residence time of MTX in the gastrointestinal tract. A polymorphism in the saturable transporter-reduced folate carrier 1 (RCF1) and/or the proton-coupled folate transporter (PCFT) has been identified. It would account for the significant inter-individual variation in absorption of MTX [8], delayed absorption thus resulting in sustained persistence of MTX in the lumen of the intestine.

Prolonged hiccups have been described in patients suffering from severe erosive oesophagitis [9] gastro-oesophageal reflux, malignant dysphagia [10] or hiatus hernia, and could be differential diagnosis in the present case. Nevertheless, the brief duration, the temporal relationship between MTX and the hiccups, as well as the absence of any gastrointestinal and neurological obvious comorbidities are consistent with an adverse drug reaction (note that no gastroscopy has been performed).

Hiccups are an atypical manifestation during rheumatic conditions and may represent a more severe course of gastro-oesophageal disease. MTX is probably underestimated as a cause of hiccups, leading to significant distress and discontinuation of medication. Finally, the present case also provides evidence that MTX-induced oral toxicity and ancillary hiccups can be by-passed by parenteral administration.
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Letters to the Editor

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Distinguishing between the innate immune response due to ocular inflammation and infection in a child with juvenile systemic granulomatous disease treated with anti-TNF-α monoclonal antibodies

Sr., Early-onset sarcoidosis (EOS) is often diagnosed if there is granulomatous involvement of an organ or sometimes as a diagnosis of exclusion in a child presenting with fever, rash and swollen joints. Recent evidence points to the fact that EOS is synonymous with juvenile systemic granulomatous disease (JSGD), also eponymously known as Blau syndrome (BS) or Jabs disease [1, 2]. They share clinical features of uveitis, dermatitis and arthritis, and are caused by inherited (BS) or sporadic (EOS) mis-sense mutations in the NACHT (NAIP (neuronal apoptosis inhibitory protein), CIITA (MHC Class II transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein) protein domain of the NOD2 (CARD15) gene, a major orchestrator during innate immune responses [1, 3].

Granulomatous disease of any origin may cause a panuveitis characterized by inflammation in the anterior and vitreous chambers and also the choroid or retina. We report a case of JSGD with a novel mutation and highlight the difficulty in distinguishing between granulomatous inflammation and infection in ocular inflammation. The importance of this is magnified when anti-TNF-α agents are implicated. We also speculate on mechanisms by which infection and inflammation may share a similar clinical profile.

A 15-month-old Caucasian male, C.P., presented with a 2-week history of spiking fevers, a follicular, erythematous rash and symmetrical polyarthritis affecting the small joints of hand, ankles, knees and wrists and hips (Fig. 1). He had normocytic anaemia (7 g/dl), normal ferritin and elevated ESR and CRP (100 mm; 200 mg/l). Autoantibodies including RF and ANA were negative and infection was excluded. Biopsies were not taken from skin or SF.

A clinical diagnosis of systemic-onset JIA was made initially followed by treatment with MTX, IVIG and anakinra alongside frequent, intermittent courses of oral, IA and i.v. CS therapy for recurrences of rash and arthritis over the next 4 years. Consequently, etanercept and MTX were instituted when C.P. was 6 years old. Etanercept was stopped upon developing bilateral anterior uveitis [4]. In order to control both ocular disease and arthritis, adalimumab was started but 8 weeks later, C.P. was admitted as an emergency with papilloedema and raised CSF pressure, CSF leucocyte count and protein. Investigations for tuberculosis were negative including CSF PCR, CSF and blood culture, ELISpot™ (Mabtech, Nacka, Sweden) IFN-Ɣ-release assay (IGRA) and TST (tuberculin skin test). Despite negative results, he was treated empirically with a full course of quadruple therapy for tuberculous meningitis and adalimumab was stopped.

Ocular inflammation relapsed during anti-tuberculous therapy with reduction of vision attributable to panuveitis [4] with choroidal infiltrate; this responded to oral CS and MTX. Aqueous fluid was sampled under general anaesthetic for MTb PCR but the sample volume was insufficient.

At this stage, we revised the differential to consider inflammatory granulomatous diseases as neither granulomatous ocular disease nor recurrent rash are consistent

References

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