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NSAID hypersensitivity in twins

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Abbreviations

NSAIDs: nonsteroidal anti-inflammatory drugs

DPT: drug provocation test

CU: chronic urticaria

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COX-1:cyclooxygenase-1; COX-2: cyclooxygenase-2

BAT: Basophils activation test

Dear editor,

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most prescribed drugs in the world. They may cause up to 25% of reported adverse drug events, which comprehend immunologic and non-immunologic hypersensitivity reactions and affect approximately 0.6% to 2.5% of the general population [1].

In recent years, the interest on the genetic mechanisms involved in hypersensitivity drug reactions has increased. Genes coding for enzymes and receptors in the prostaglandin and leukotriene pathways are often responsible for NSAIDs hypersensitivity [2,3]. Several studies on possibly involved genes have been performed and have widened the knowledge on NSAIDs hypersensitivity [4]. However, so far, the international literature has not analyzed the possibility of a familial inheritance of NSAIDs hypersensitivity. We describe here the case of two homozygous fifteen year-old twin sisters who presented the same kind of hypersensitivity reactions to NSAIDs [2].

Both twins presented a hypersensitivity reaction to Ibuprofen, characterized by facial swelling, approximately eleven hours after the drug intake, five years before they came to our Unit. They both were taking the drug because of fever. The reaction spontaneously disappeared after two hours. For this reason, we hospitalized them to perform a drug provocation test (DPT). As shown by the study conducted by Çelik et al., DPTs are to be preferably performed in a safe environment provided with emergency equipment and experienced professionals, and where patients can be observed for a certain amount of time in order to treat possible severe drug reactions [5]. The first twin (A), who did not have a history of atopy or chronic urticaria (CU), underwent a DPT to ibuprofen (maximal dose: 752 mg) to confirm the diagnosis. On the contrary, the second twin (B), who presented with a history of allergy to birch and hazel and who suffered from CU, was investigated for an alternative NSAID, since CU is a well-known risk factor for developing hypersensitivity reactions to analgesic drugs that mainly inhibit the COX-1 pathway [5,6]. She underwent a DPT to piroxicam (maximal dose: 36 mg). Twin A did not develop any clinical manifestation during the observation period. Nevertheless, the morning after the test, she presented with labial swelling and urticaria localized on her left arm. During the observation period, twin B presented a mild serous rhinitis and a modest left eyelid swelling, with no conjunctivitis associated,

which actually worsened the day after the test, when labial swelling appeared as well. The two provocation tests were therefore considered as positive for both sisters.

Tryptase concentrations were stable in both twins before and after the tests (A: from 6.51 ug/L to 5.79 ug/L; B: from 5.94 ug/L to 5.51 ug/L). On the contrary, histamine blood levels significantly increased in both patients (A: from 0.58 ng/mL to 1.91 ng/mL; B: from 0.58 ng/mL to 1.28 ng/mL). Basophil activation test (BAT) resulted negative to ibuprofen for twin A. It was negative to both ibuprofen and piroxicam for twin B. Even though BAT seems to have low sensitivity and specificity for NSAIDs, we run it to complete the allergy work up in our patients. Blood samples for BAT were collected six weeks after the provocation tests, right before the twins came in our Unit to continue the investigations.

Indeed, six weeks after the first test, another DPT to a COX-2 selective NSAID (celecoxib) was carried out for both sisters, in order to find a therapeutic alternative. Five hours after the beginning of the DPT to celecoxib (administered dose: 4.7 mg/kg for a cumulative dose of 235 mg), twin A started to present facial and inferior lip swallow. Tryptase levels remained stable after the test (from 4.43 ug/L to 4.80 ug/L), while histamine concentration increased (from 0.91 ng/mL to 3.42 ng/mL). It was not possible to perform a BAT for celecoxib due to basophils hyper-reactivity at basal state, even 6 weeks after this second DPT. Such a hyper-reactivity was not detected when the first BAT was performed in this patient.

Five and a half hours after the beginning of the DPT to celecoxib (administered dose: 4.7 mg/kg for a cumulative dose of 235 mg), twin B started to present facial swallow. Tryptase blood levels were stable before and after the test (from 5.06 ug/L to 3.41 ug/L). Histamine concentration increased after the DPT (from 0.23 ng/mL to 4.43 ng/mL). BAT for celecoxib resulted positive. Blood samples for BAT were collected 6 weeks after this second DPT.

The fact that the two girls showed a hypersensitivity reaction even to an anti COX-2 drug, brought us to conclude that no NSAID alternatives could be found.

The study conducted by Asero in 2002 showed that NSAIDs hypersensitivity may precede the onset of CU [7]. In fact, we discovered that twin A had developed CU two weeks after the first positive DPT. CU is a skin disorder that can be elicited by numerous factors, and NSAIDs in particular. Furthermore, the pathogenesis of CU is not fully understood but genetic factors are believed to play a very important role in its development and progression [8]. A study in a large population of patients with CU revealed a higher prevalence of CU in first-degree relatives than in the general population [8,9].

As for the CU presented by the twins, possible causes were investigated. They were both euthyroids with negative anti-thyroid antibodies. They had negative serology for Mycoplasma and Helicobacter Pylori infection. Their parents did not refer a history of CU. We also searched for the presence of autoantibodies directed towards the alpha subunit of the high-affinity IgE receptor (Fc α RI) of mast cells and basophils which resulted negative in both twins. These autoantibodies were found in approximately 40% of subjects with CU in a study conducted by Saini [10]. Although they are not specific for CU and the assays used for their detection are not specific for them, their presence is thought to be pathogenic for CU. Specific differences in the expression of Fc α RI-signaling molecules in the basophils or mast cells of CU patients may also lead to the onset of urticaria eruptions [10].

In conclusion, the international literature reports that CU predisposes to hypersensitivity reactions to NSAIDs and is genetically inherited principally in first-degree relatives. On the other hand, NSAIDs hypersensitivity may lead to the onset of CU and is genetically determined. With our report we support the existence of a familial inheritance of the genetic mechanism causing NSAIDs hypersensitivity for which further investigations are needed.

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