Folic acid allergy and the role of the basophil activation test

Alergia ao ácido fólico e o papel do teste de ativação de basófilos

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ABSTRACT

***Background**: Despite the large use of folic acid supplements, there are very few cases of reported allergy.* ***Clinical case**: A 38-year-old woman, experienced palmoplantar pruritus, generalized urticaria, angioedema and conjunctival hyperemia, 30 minutes after the intake of a 5mg folic acid tablet. She was taken to the Emergency Department and on discharge was referred to the Allergy and Clinical Immunology Department, where the patient underwent a diagnostic workup. The Skin Prick Test (SPT) was positive for the 5 mg/mL concentration and the Basophil Activation Test (BAT) was considered positive for both dilutions, from an initial solution concentration of 5mg/ml: 1/100 dil (CD63=9.03%; SI=10.1) and 1/160 dil (CD63=7.46%; SI=8.4).* ***Discussion/ Conclusion**: We report a patient with an immediate reaction to folic acid with positive SPT and BAT, which favors an IgE-mediated allergy. To our knowledge, this is the first case describing the use of a BAT in the diagnostic workup of folic acid allergy.*

***Keywords:** Basophil activation test, drug allergy, folic acid.*

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RESUMO

Introdução: Apesar da grande utilização de suplementos de ácido fólico, existem poucos casos de alergia relatados. **Descrição do caso**: Mulher de 38 anos, que apresentou prurido palmoplantar, urticária generalizada, angioedema e hiperemia conjuntival 30 minutos após a ingestão de um comprimido de ácido fólico de 5mg. Foi levada ao serviço de urgência e, à data de alta, referenciada para o serviço de imunoalergologia para realização de estudo. O teste cutâneo por picada (TCP) foi positivo para a concentração de 5 mg/ml e o teste de ativação de basófilos (TAB) foi considerado positivo para ambas as diluições, a partir de uma concentração inicial de 5mg/ml: 1/100 dil (CD63=9,03%; SI=10,1) e 1/160 dil (CD63=7,46%; SI=8,4). **Discussão/conclusões**: Descrevemos uma doente com uma reação imediata ao ácido fólico com TCP e TAB positivos, o que favorece uma alergia IgE-mediada. Tanto quanto sabemos, este é o primeiro caso a descrever a utilização do TAB no estudo da alergia ao ácido fólico.

Palavras-chave: Ácido fólico, alergia a medicamentos, teste de ativação de basófilos.

Folate is naturally present in many foods, including vegetables, fruits, beef liver, nuts, beans and peas. Folic acid is a synthetic form of vitamin B9 and it is chemically distinct from natural folates. It is metabolically inactive and needs to be metabolized to 5-methyl-THF, after which it behaves identically to natural dietary folate[1]. It can be incorporated into food during production process to enhance grain-based products such as bread, flours, pastas, rice, and cornmeal, and can also be present in certain dietary supplements.

The recommended daily amount of folate for adults is 400 micrograms[2]. In order to have higher bioavailability at the intestinal brush board, the synthetic form of folic acid only contains the monoglutamate conjugate[3].

Adequate levels of folic acid are needed during pregnancy to help prevent neural tube defects such as anencephaly and spina bifida. Women who are planning a pregnancy are advised to take 400 µg of folic acid daily, starting at least 1 month before pregnancy[4].

Hypersensitivity reactions to an essential food component such as folic acid are rare. Only a few cases have been reported in the literature, with the first one described in 1949[5].

We present a 38-year-old woman with a history of an allergic reaction following the initiation of oral folic acid intake for pregestational supplementation.

In 2021, 30 minutes after the first intake of a 5mg folic acid tablet (Folicil 5mg, BIAL) as recommended by her Obstetrician, she experienced palmoplantar pruritus, generalized urticaria, periocular angioedema and conjunctival hyperemia. She promptly took an oral antihistamine with no clinical improvement and was taken to the Emergency department where she was treated with intravenous steroids and antihistamines, with complete symptom resolution after a few hours. Upon discharge she was advised to avoid folic acid supplements and was referred to the Allergy and Clinical Immunology Department for further investigation.

The patient's personal and family history was unremarkable and denied any prior adverse drug reactions, food allergy (including food that are fortified with folic acid) or other allergic diseases. Following a thorough

anamnesis and after providing informed consent, the patient underwent a diagnostic workup, consisting in skin prick test (SPT) and a basophil activation test (BAT).

Dilutions were prepared under laminar flow, grinding pills of folic acid (Folicil 5mg, BIAL) to a very fine powder and proceeding to sequential dilutions in sterile 0.9% saline solution. Suspensions were prepared at 5mg/mL (1:1) for SPT[3,5,9] and at 0.05mg/L (1:100) and 0.03123mg/mL (1:160) to perform the BAT, considering the solubility of the folic acid[6]. Dilutions at 1:100 and 1:160 were submitted to sterilizing double filtration at the end of preparation with filter 0.22 µm.

The SPT with a 5 mg/ml suspension resulted positive with a wheal of 6 mm. Five control subjects underwent SPT with the same dilution and had a negative result. For that reason, no IDT were done.

To perform the BAT, we used a 0.05 mg/ml (1:100) and a 0.03125 mg/ml (1:160) solutions and the analysis was made by flow cytometry, using the FLOW CAST® Basophil Activation Test (Flow cast, Buhlmann, City, Switzerland) according to the manufacturer's instructions.

Basophils were gated based on the constitutive expression of the chemokine receptor CCR3, using a monoclonal antibody labelled with phycoerythrin (CCR3-PE). The activation marker CD63 (gp53) expression on basophils was measured using an anti-CD63 labelled with fluorescein isothiocyanate (CD63-FITC), before and after cell stimulation. Results were reported as percentage of basophils expressing CD63 and the ratio between stimulated and non-stimulated cells. Positivity was defined as >5% of basophils expressing CD63 and a stimulation index (SI) >2.

The patient's BAT with folic acid was considered positive for both solutions: 0.05 mg/ml (1:100) (CD63=9.03%; SI=10.1) and 0.03125 mg/ml (1:160) (CD63=7.46%; SI=8.4) (Figure 1).

The diagnostic workup favors a diagnosis of an IgE mediated allergy to folic acid. The patient was advised to abstain synthetic folic acid and keep a diet rich in natural folates to provide adequate nutrition. Since then, the patient did not have any other episode of urticaria/angioedema.

Despite the widespread use of folic acid supplements, there have been very few reported cases of allergy. Reactions to folic acid have been described after oral and intravenous administration with clinical manifestations ranging from recurrent urticaria to anaphylactic shock[5].

In most cases where folic acid allergy is reported, patients tend to tolerate folic acid from natural sources. This suggests that the active folic acid ingredient in natural foods may have been rendered non-allergenic by food processing or that antigens are either absent or concealed in these products[7]. Another hypothesis suggests that dietary folic acids, in their polyglutamate form, have lower bioavailability[8].

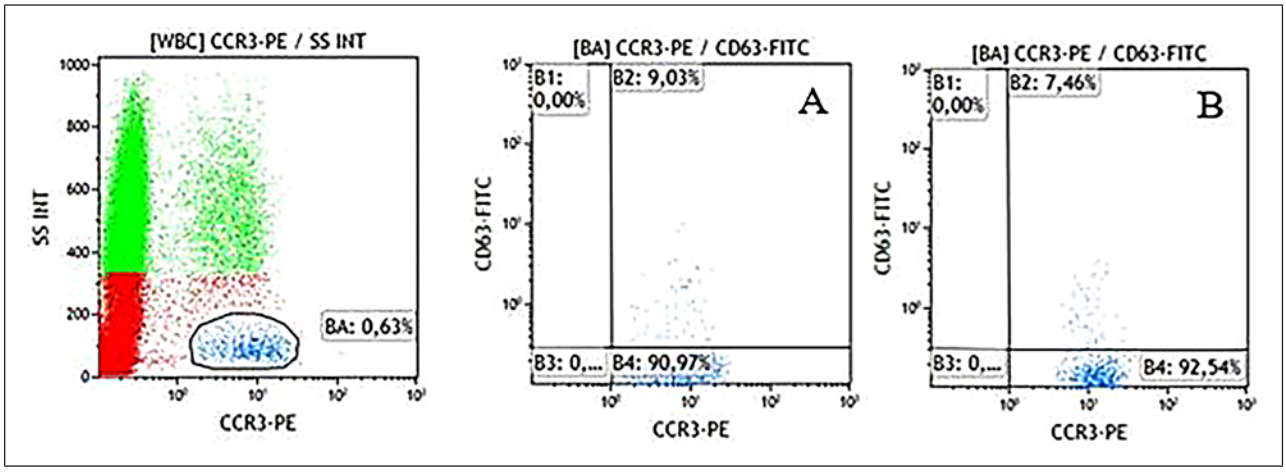

Figure 1. CD63 expression on basophils stimulated with folic acid in both solutions – A (1:100) and B (1:160).

Most of the reported cases in the literature were substantiated by positive SPT[3,5,9,10,12]. Although the low molecular weight of folic acid prevents it from being recognized as a full allergen when isolated, its ability to produce a positive immediate skin test suggests that is capable of rapidly combining with self-proteins or polypeptides in the skin to form a complete allergen[10].

Currently, BAT is applied in research settings, and it can be a useful and safe complementary *in vitro* test, allowing to confirm the diagnosis without the risks of an oral provocation test, especially in subjects experiencing serious systemic reactions[11]. However, the diagnostic accuracy of BAT with folic acid requires further study.

Oral provocation tests with folic acid have been described[12]. However, in this case, given the patient's history consistent with an immediate reaction and positive results from the diagnostic workup, an oral provocation test was not performed.

In conclusion, folic acid allergy is a rare condition. We present a patient exhibiting an immediate reaction to folic acid, supported by positive results both from SPT and BAT, suggesting an IgE-mediated allergy. To our knowledge, this is the first reported case describing the application of a BAT in folic acid allergy.

Conflict of interest

The authors have no conflict of interest to declare.

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