Hypersensitivity reactions to folic acid: Three case reports and a review of the literature

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Abstract
Adverse reactions to folic acid are an extremely uncommon condition; we present three cases of hypersensitivity to folic acid with different symptomatic manifestations. In the first and second cases, we made the diagnosis of IgE-mediate-type allergy to folic acid, while in the third one, we found a fixed drug eruption to folic acid.

Keywords
drug allergy, fixed drug eruption, urticaria

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Introduction
Folic acid (vitamin B11) is essential to numerous bodily functions ranging from nucleotide biosynthesis to the remethylation of homocysteine. It is especially important during periods of rapid cell division and growth. Both children and adults require folic acid to produce healthy red blood cells and prevent anemia.

It is composed of a non-reduced aromatic pteridine ring linked to para-aminobenzoic acid and one or more glutamic residues.

Our mean dietary intake is around 247–291 µg per day. Dietary folic acid is mainly the polyglutamate conjugate and it is slowly broken down into the monoglutamate form in the small intestine. The synthetic form contains only the monoglutamate conjugate, resulting in higher bioavailability and bypassing the need for removal of the polyglutamate conjugate at the brush border. In the enterocyte, monoglutamate folic acid is reduced, methylated, and released into the bloodstream as 5-methyltetrahydrofolate monoglutamate. However, these mechanisms are saturable, and unmetabolized synthetic folic acid can be detected in blood at doses as low as 200 µg. In blood, metabolization occurs after cellular uptake in much the same way as after intravenous administration of folic acid.

Adverse reactions to folic acid are an extremely uncommon condition, but in literature, 13 cases (all female subjects, but 1) of hypersensitivity are described from 1949.

We present three additional cases of hypersensitivity to folic acid with different symptomatic manifestations (every patient gave informed signed consent to perform allergy evaluation and to show their data for publication).
Case report 1

In the first case, we present a 47-year-old woman with severe anemia. Since folic acid is essential for heme synthesis, she started therapy with this drug. After the third day of treatment with folic acid (5 mg, commercially available formulation) and SiderAL® (vitamin B12, vitamin C, and iron complex), she experienced generalized urticaria. Her symptoms receded in few hours only with oral antihistamines. The next day the patient took the same therapy again and presented identical manifestations.

She had a long history of allergic rhinoconjunctivitis (grass pollen and wall pellitory), but she was not symptomatic when she had the reactions and she did not refer any adverse drug reaction.

So the patient underwent a complete diagnostic allergological workup, consisting in skin prick test (SPT) and intradermal test (IDT) to several dilutions of the crushed folic acid pill and iron and vitamins complex. The SPT resulted positive to folic acid 5 mg/mL dilution in our subject and negative in 10 controls. Moreover, we dosed baseline serum tryptase that was normal to exclude an underlying mastocytosis. To exclude the role of iron and vitamins complex, the patient performed an oral provocation test (OPT) with this drug with negative result. Therefore, we concluded with a diagnosis of IgE-mediated-type allergy to folic acid.

Case report 2

We present a 66-year-old man with severe anemia, who experienced acute urticaria and loss of consciousness after 15 min from taking folic acid (Folifill® 5 mg). Transferred to emergency department, he was treated successfully with intravenous steroids and antihistamines. In his clinical history, he did not refer any adverse drug reaction or other allergic manifestations.

His complete diagnostic allergological workup (performed with the same features of the previous patient) showed a positive SPT to folic acid 5 mg/mL dilution. Also, in this patient, we excluded other comorbidities (e.g. mastocytosis) that could explain the severe referred anamnestic reaction. So we performed an OPT with this drug with positive result. Also in this case, we concluded with a diagnosis of IgE-mediated-type allergy to folic acid.

Case report 3

In the third case report, we present the medical history of a 40-year-old woman with a round erythematous-violaceous well-defined macula on the left iliac spine associated with itching and burning that appeared after 15 days of folic acid therapy (Folina or Inofolic Plus®); the lesion resolved without any residual pigmentation after 7 days from therapy interruption.

She did not have any history of allergic disease. So we suspected a fixed drug eruption (FDE) on the basis of the referred clinical manifestation and performed a complete allergological workup to make this kind of diagnosis. Normally, the diagnosis is clinical and histological. The identification of the responsible drug can be obtained as follows:

- Accurate collection of medical history;
- Patch test;
- OPT.

The OPT consists in the administration of the suspected drug with divided doses (1/10, ¼, ½, 1, 2 doses) every 6–12 h. The test is positive if we observe a reactivation of the lesions or appearance of new spots in other locations. Although this test is considered the gold diagnostic test, the patch test is more extended for its simplicity, speed, and safety. It is performed 6–8 weeks after the acute reaction and consists in the application of the drug, in appropriate concentrations, at the level of the previously affected sites, but also to healthy skin; the occlusion lasts about 24 h. The test is positive if the patient experiences itching, erythema, papules, and eczema (normally only on the skin site of the lesions). Our patient underwent folic acid SPT and then folic acid patch test on the healthy and damaged skin; each test was negative.

The next diagnostic step was the folic acid OPT; a month later of the interruption of folic acid intake, after obtaining informed consent, the patient was challenged with this drug with the reappearance of the lesion on the same site.

Based on the clinical history and positive OPT, we definitively diagnosed a case of FDE after use of folic acid (the patient refused the histological exam).

Discussion

We showed three case reports of drug hypersensitivity after oral administration of folic acid, but
reactions have been reported also after the ingestion of fortified food with very low content of folic acid. In a case report of 2015, Schrijvers et al.,\(^1\) in fact, showed the case of anaphylactic shock after intake of folic acid and other drugs in a woman who referred pruritus, flushing, and diarrhea and needed to lie down after ingestion of beverage or food fortified with vitamins and folic acid.

In all the cases of hypersensitivity, the great majority of subjects tolerated folic acid from natural sources. This leads to a speculation that the active principle of folic acid in natural foodstuff may have been rendered non-allergenic by food processing or that the antigens are absent or occult in these products.\(^5\) Another hypothesis\(^12\) speculates that the dietary folic acids, being the polyglutamate form, had a minor bioavailability.

About the clinical expression, this hypersensitivity ranges from recurrent urticaria–angioedema\(^3,5\) to anaphylactic shock.\(^1,4,7,10,11\) In a case report, Sesin and Kirschenbaum\(^8\) reported a reaction characterized by a febrile episode with itching, urticaria, and generalized pain, while Roy and Roy\(^6\) described a delayed pruritic rash occurring 3 days after the intake of a multivitamin complex.

The anaphylaxis cases are assumed to be forms of immediate-type allergy because IgE antibodies to folic acid are detected in the patient’s serum.\(^2,9\) Folic acid is thought to be able to act as a hapten in immunogenic reactions, corresponding with its low molecular weight (441 Da), well below the 1000 Da threshold usually required for an agent to be recognized as a complete antigen or allergen. The ability of folic acid solutions to elicit positive immediate skin test reactions suggests that folic acid must be capable of rapidly combining with self-proteins or polypeptides in the skin to form a complete allergen.\(^2\)

None of the studies described cases of FDE after use of folic acid; so we added a new clinical form of adverse reaction to folic acid to the literature.

In conclusion, since folic acid allergy is a rare condition, it should be suspected in cases of chronic urticaria and unexplainable anaphylaxis. So in these cases, a proper evaluation should be started quickly. Overall, in the case that folic acid is available without prescription, the physician should be more careful in patients who use this drug.

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