

THERAPEUTIC HOTLINE

Oral iron therapy and chronic idiopathic urticaria: sideropenic urticaria?

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ABSTRACT: Chronic urticaria (CU) is frequent, remains often idiopathic despite diagnostic efforts, and sometimes poorly responds to oral antihistamines and/or corticosteroids. We noticed that hyposideremia is often found in patients with chronic idiopathic urticaria poorly responsive to usual treatments (prCIU), and oral iron therapy is frequently associated to improvement or resolution of urticaria. Between 2003 and 2012, we observed 122 patients with prCIU, of which 81 had moderate hyposideremia at our first visit. They continued the antihistamines already practiced and received oral iron therapy for 30 or 45 days. Two months after our first visit, all had normal serum iron levels; 64 reported complete remission of urticaria and 17 reported improvement superior to 80%. No adverse reactions to treatment were observed. Follow-up visits confirmed stability of results over 6 months. Our preliminary data show that hyposideremia is the only abnormality in many patients with prCIU, and restoration of normal iron serum levels is associated to remission or remarkable clinical improvement of urticaria. In consideration of low cost and potential benefits for some patients, determination of serum levels of iron could be introduced in the diagnostic workup of chronic urticaria, maybe as a second-level exam in patients without other relevant clinical or laboratory abnormalities.

KEYWORDS: chronic idiopathic urticaria, hyposideremia, oral iron therapy

Introduction

Chronic urticaria (CU) affects about 1% of the general population, may be intensely pruritic and interfere with daily activities or sleep; antihistamines and/or corticosteroids are sometimes insufficient to induce complete remission. Despite careful clinical investigation and extensive laboratory screening, CU remains often idiopathic and treatment ineffective (1–5). We report our 10-year

experience about frequent association between hyposideremia and chronic idiopathic urticaria (CIU) poorly responsive to treatment with oral antihistamines and/or corticosteroids (prCIU); in many cases, restoration of normal serum iron concentration with adequate oral iron therapy led to resolution or remarkable improvement of urticaria.

Methods

We reviewed the clinical files of patients with prCIU observed between January 2003 and December 2012. CU was defined as the presence of hives for at least six consecutive weeks (1), and

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Table 1. Scoring system of urticarial signs and symptoms

Number of wheals	Score	Mean diameter of wheals	Score	Pruritus	Score	Number of days per week with urticaria	Score
None	0	No wheals	0	Assessed using a visual discrete scale (0 = not present, 5 = severe)	0	0	0
<15	1	<2 cm	1		1	1	1
15–30	2	2–3 cm	2		2	2	2
31–45	3	>3 to 4 cm	3		3	3–4	3
46–60	4	>4 to 5 cm	4		4	5–6	4
>60	5	>5 cm	5		5	7	5

The final severity score of urticaria is the sum of the four parameters.

Table 2. Standard set of laboratory exams performed in the diagnostic process of urticaria.

Hematocrit	Urinalysis
Hemoglobin level	Examination of stools for parasites
White blood cell count	Examination of stools for occult blood
Differential blood cell count	Serum levels of glucose
Total eosinophil count	Serum levels of proteins
Liver and kidney function tests	Serum levels of complements
Erythrocyte sedimentation rate	Serum levels of iron
Serum levels of C reactive protein	Serum levels of ferritin
Anti streptolysin titer	Serum levels of transferrin
Thyroid function test	

severity was defined using the scoring scheme shown in Table 1. Diagnostic procedure included, in agreement with previous studies (2), detailed history taking and complete physical examination to find possible signs/symptoms of dermatologic, odontostomatologic, otorhinolaryngologic, gastroenterological, allergic, autoimmune, rheumatological, hematological, endocrine, infectious, cardiovascular, respiratory, renal/urinary, genital, and/or neuropsychiatric conditions, in cooperation with the appropriate specialists, who also suggested, when necessary, investigations to be performed in addition to the standard set of laboratory exams shown in Table 2. Urticaria was defined idiopathic when all diagnostic procedures failed to identify known causes.

Finally, urticaria was defined as poorly responding to treatment when oral antihistamines for at least four consecutive weeks and corticosteroids for up to 1 week, administered in agreement with the international guidelines available at the time of

Table 3. Characteristics of patients enrolled in the study, all suffering from chronic idiopathic urticaria poorly responsive to treatment with oral antihistamines and/or corticosteroids

Total number of patients	122
Males	47
Females	75
Age (years) at our first visit	
Mean $\pm$ standard deviation	42.47 $\pm$ 8.49
Range	27–55
Patients referred to our center by	
General practitioners	91
Dermatologists	10
Other specialists	21
Duration of urticaria at our first visit (weeks)	
Median	13
Range	11–15
Severity score of urticaria at our first visit	
Patients with hyposideremia (n = 81)	
Mean $\pm$ standard deviation	11.21 $\pm$ 2.64
Range	8–19
Patients without hyposideremia (n = 41)	
Mean $\pm$ standard deviation	11.44 $\pm$ 2.87
Range	8–20

visit, yielded a decrease of severity score inferior to 20% from baseline (start of treatment).

Results

In the period 2003–2012, we observed 122 patients with prCIU (Table 3). Complete diagnostic procedure showed normal clinical and laboratory results for 41 patients (group A), and only moderate hyposideremia in 81 (group B).

Upon our suggestion, all patients continued oral antihistamines that they were already taking at the

time of our first visit; hyposideremia was treated with 105 mg/day of elemental iron, taken as ferrous sulfate. At first follow-up visit (T1), after 1 month of treatment, improvement of urticaria was 20–30% in group A and >80% (with 43 cases of clinical remission) in group B. Patients of group B showed normal serum iron concentrations on this occasion; noteworthy, values close to the lower limit of normal were often associated with less remarkable improvements.

Patients of group A were redirected to alternative treatments. Patients of group B were instructed to discontinue antihistamines; additional oral iron therapy for 15 days was suggested in 15 cases where serum iron concentration was in the lower 10% of normal range, i.e., between n_{min} and $n_{min} + 0.1 (n_{max} - n_{min})$, where n_{min} and n_{max} are the lower and upper normal values, respectively (e.g., between 60 and 71 µg/dL with 60–170 as normal range). At second follow-up visit (T2), 1 month after T1, none of the 81 patients of group B had hyposideremia or serum iron levels in the lower 10% of normal. Of the 15 who had received iron supplementation for 45 days, eight reported remission of urticaria and seven reported further improvement from T1 (85–90% from our first visit). Among the 23 with partial remission at T1, 13 reported complete remission and 10 did not report variations of their clinical picture. Finally, the 43 patients with complete remission at T1 did not report further urticarial episodes.

No adverse reactions were observed during the entire treatment. Follow-up visits, 3 and 6 months after T2, confirmed stability of clinical picture and levels of serum iron in all of the 81 patients.

As hyposideremia is a rather common condition, we asked our laboratory to select a sample of 122 healthy subjects, exactly sex and age matched with our study population and observed in the same time frame, to be used as control group. Prevalence of hyposideremia in these subjects was 21/122, significantly ($p < 0.001$, chi-squared test) inferior to that found among prCIU patients.

Discussion

Few studies exist on association between hyposideremia and CU. As of November 25, 2013, a PubMed search with the string “iron AND urticaria” yields two relevant results. One reports the finding of hyposideremia in 22 of 77 patients with CU, with some complete remissions or improvements after iron supplementation (6), the other is a 6-week study on five young women with mild-to-moderate

iron deficiency anemia and CU due to nickel sensitivity, of which three, treated with low nickel diet and 150 mg/day of iron, achieved complete and stable remission of urticaria after 3–4 weeks, whereas the other two, treated only with low nickel diet, had partial improvement (7).

Our study population is quantitatively larger and also qualitatively different, because it includes only patients without known causes of urticaria and poorly responding to oral antihistamines and corticosteroids. In the first of the aforementioned studies (6), statistics included patients with CU of any origin, and this could explain the reported frequency of hyposideremia of ~28.6%, remarkably lower than the ~66.4% in the present study.

Our data show that a surprisingly large subgroup of 122 patients with prCIU had hyposideremia, and that all 81 patients in this subgroup achieved remission or considerable improvement of urticaria after restoration of normal serum iron levels with adequate oral iron therapy.

Despite some limitations due to the open, retrospective nature of our study, and even taking into account that hyposideremia is not an unusual finding in any sample of population, our final results are unlikely to be coincidental, considering the number of cases, the consistency of data and the highly significant difference from controls: they outline a clinical picture that could be defined as “sideropenic urticaria,” and let us hypothesize a causal correlation between hyposideremia and CIU in some patients. An exact pathogenic mechanism cannot be currently stated, also because CIU results from a complex interplay of several individual and environmental factors. Some literature data let us think that transferrin could be one of the elements involved in such interplay. Theobald et al. (8) experimentally demonstrated that transferrin, through an unknown mechanism, inhibits histamine release from mast cells, and such activity depends on its degree of iron saturation (higher saturation yields higher inhibition of histamine release). On such basis, it could be hypothesized that hyposideremia, which reduces iron saturation of transferrin, may lower the threshold of stimulation required to trigger mast cell degranulation, thus predisposing to development of urticaria in response to mild, normally harmless stimuli, which easily occur in everyday situations. This hypothesis deserves, in our opinion, future experimental investigation.

Regardless of the possible mechanism, our clinical experience is that in patients with prCIU and hyposideremia not associated to anemia or alteration of serum transferrin or ferritin, restoration of

normal serum levels of iron is associated with remission or significant improvement of urticaria, which remains stable in the 6 months after discontinuation of any treatment. Based on these initial data, while highlighting that further studies are necessary to better define terms and possible reasons for this fact, we believe that determination of serum levels of iron could be introduced in the diagnostic workup of CU, maybe as a second-level exam in patients without other relevant clinical or laboratory abnormalities, in consideration of its relatively low cost and potential benefits for some patients.

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