Recurrence of chronic urticaria caused by reinfection by *Helicobacter pylori*

Recidiva de urticária crônica decorrente de reinfecção por Helicobacter pylori

Recidiva de urticaria crónica decurrente de reinfección por Helicobacter pylori

Dayanne Mota V. Bruscky[1], Luiz Alexandre R. da Rocha[1], Aldo José F. Costa[2]

ABSTRACT

Objective: To describe a case of chronic urticaria in a female adolescent associated with *Helicobacter pylori* infection, confirmed in two different occasions, with improvement of urticaria after the antibacterial treatment.

Case description: A 13-year-old female patient sought medical care with chronic urticaria and epigastric pain unresponsive to medical treatment. Laboratorial tests for further investigation were normal except for the upper gastrointestinal endoscopy with biopsy showing moderate chronic active gastritis associated with *Helicobacter pylori*. After specific and appropriate treatment, the patient had remission of the symptoms. A new upper gastrointestinal endoscopy to control the treatment after nine months was normal. After five years, the patient returned with recurrence of urticaria and epigastric pain. She was taking antihistamines, without any improvement. It was again submitted to screening protocol for chronic urticaria with normal results. She was submitted to upper gastrointestinal endoscopy, which showed positive urease test. The patient started a new treatment for *Helicobacter pylori* with disappearance of chronic urticaria and epigastric pain within seven days.

Comments: The reported case suggests a causal relationship between the positive diagnosis of *Helicobacter pylori* and the occurrence of chronic urticaria, showing the remission of symptoms after the institution of effective therapy for this agent. Chronic urticaria is a disease of complex etiology, and although controversial, there is growing evidence of *Helicobacter pylori* involvement with extraintestinal diseases, including chronic urticaria.

Key-words: urticaria; *Helicobacter pylori*; adolescent.

RESUMO

Objetivo: Descrever, em uma adolescente do sexo feminino, o caso clínico de urticária crônica associado à infecção por *Helicobacter pylori* confirmado em dois momentos distintos, com melhora após a terapêutica antibacteriana.

Descrição do caso: Paciente do sexo feminino, 13 anos, procurou atendimento médico com urticária crônica e dores epigástricas sem resposta ao tratamento medicamentoso. Os exames solicitados para investigação complementar apresentaram-se normais, exceto a endoscopia digestiva alta com biópsia, que evidenciou gastrite crônica ativa moderada associada ao *Helicobacter pylori*. Foi iniciado o tratamento adequado para a bactéria em questão e a paciente apresentou remissão dos sintomas. Nova endoscopia digestiva alta para controlar o tratamento após nove meses estava normal. Cinco anos depois, a paciente procurou novamente o ambulatório queixando-se de retorno do quadro de urticária e dores epigástricas. Ela se encontrava em uso de anti-histamínico, sem melhora. Foi novamente submetida a protocolo de exames para investigar urticária crônica, com resultados dentro da normalidade. Foi submetida à endoscopia digestiva alta, que apresentou teste da urease positivo. Iniciou-se então novo tratamento para *Helicobacter pylori* por sete dias, com desaparecimento da urticária crônica e das dores epigástricas.

Comentários: O caso relatado sugere relação causal entre o diagnóstico positivo para o *Helicobacter pylori* e a ocorrência do quadro de urticária crônica, com instituição de terapêutica eficaz para tal bactéria e remissão dos sintomas. A urticária crônica é uma doença de etiopatogenia complexa e, apesar das controvérsias, as evidências do envolvimento do *Helicobacter pylori* com doenças extraintestinais vêm crescendo, entre elas a urticária crônica.

Palavras-chave: urticária; *Helicobacter pylori*; adolescente.

Instituição: Centro de Pesquisas em Alergia e Imunologia do Hospital das Clínicas da Universidade Federal de Pernambuco (UFPE), Recife, PE, Brasil
[1]Residência em Alergia e Imunologia Clínica pelo Hospital das Clínicas da UFPE (HC-UFPE); Alergologista e Imunologista do Centro de Pesquisas em Alergia e Imunologia do HC-UFPE, Recife, PE, Brasil
[2]Doutor em Nutrição pela UFPE; Alergologista e Imunologista do Centro de Pesquisas em Alergia e Imunologia do HC-UFPE, Recife, PE, Brasil

Endereço para correspondência:
Aldo José Fernandes Costa
Avenida Engenheiro Domingos Ferreira, 2842/1.002 – Edifício Torre Madrid Residence – Boa Viagem
CEP 51020-030 – Recife/PE
E-mail: aldojfcosta@gmail.com

Conflito de interesses: nada a declarar

Recebido em: 1/5/2012
Aprovado em: 14/9/2012

RESUMEN

Objetivo: Describir, en una adolescente del sexo femenino, el caso clínico de urticaria crónica asociado a la infección por *Helicobacter pylori* confirmado en dos momentos distintos, con mejora después de la terapéutica antibacteriana.

Descripción del caso: Paciente del sexo femenino, 13 años, buscó atención médica con urticaria crónica y dolores epigástricas sin respuesta al tratamiento medicamentoso. Los exámenes solicitados para investigación complementar se presentaron normales, excepto por la endoscopía digestiva alta con biopsia, que evidenció gastritis crónica activa moderada asociada al *Helicobacter pylori*. Se inició el tratamiento adecuado para la bacteria en cuestión, y la paciente presentó remisión de los síntomas. Nueva endoscopía digestiva alta para controlar el tratamiento después de nueve meses estaba normal. Tras cinco años, la paciente buscó nuevamente el ambulatorio quejándose de retorno del cuadro de urticaria y dolores epigástricos. Ella estaba en uso de anti-histamínicos, sin mejoría. Fue nuevamente sometida al protocolo de exámenes para investigar urticaria crónica, con resultados dentro de la normalidad. Fue sometida a la endoscopía digestiva alta, que presentó prueba de ureasa positiva. Se inició entonces nuevo tratamiento para *Helicobacter pylori* por siete días, con desaparición de la urticaria crónica y de los dolores epigástricos.

Comentarios: El caso relatado sugiere relación causal entre el diagnóstico positivo para el *Helicobacter pylori* y la ocurrencia del cuadro de urticaria crónica, con institución de terapéutica eficaz para tal bacteria y remisión de los síntomas. La urticaria crónica es una enfermedad de etiopatogenía compleja y, a pesar de las controversias, las evidencias de la implicación del *Helicobacter pylori* con enfermedades extraintestinales vienen creciendo, entre ellas la urticaria crónica.

Palabras clave: urticaria; *Helicobacter pylori*; adolescente.

Introduction

Urticaria is a mucocutaneous disease characterized by erythematous, edematous and pruritic lesions of the dermis and/or hypodermis, resulting from the degranulation of mast cells and basophils and the release of inflammatory mediators, mainly histamine[1-4]. It affects from 15 to 25% of the population at some stage of life, and is classified as acute (lesions lasting less than six weeks) or chronic, when the lesions last for more than six weeks, either daily or on most days of the week[1]. Chronic urticaria (ChU) accounts for 1% of the cases of urticaria[5], especially among women in the third and fourth decades of life[6]. It is estimated that it affects from 0.1 to 3% of the children[6]. The etiologic diagnosis, whenever it can be established, is based on history, physical examination and laboratory tests specifically directed to each case. To assure the adequacy of the treatment, it is necessary to establish the etiology, to identify and avoid possible triggers, and to use drugs that specifically act on the primary cause and/or control of the symptoms. The drugs most used as the first line treatment of ChU are the H1 anti-histamines, and as second line, the corticosteroids, leukotriene antagonists, H2 anti-histamines, immunosupressors, monoclonal antibodies (omalizumab) and the intravenous human immunoglobulin[1-2].

Several etiologic factors for ChU have been described, among them the chronic infections and the parasitic infestations[1,3,7]. The infection by *Helicobacter pylori* has been the subject of investigation as a possible etiologic factor for ChU in the last few years[3,5,7-11]. *Helicobacter pillory* affects nearly 50% of the world population[12]. In Brazil, its prevalence ranges from 34 to 80% adults and children[12]. The prevalence is higher in childhood, mainly in low income regions[13].

The diagnosis of *Helicobacter pylori* infection can be established by endoscopic and non-endoscopic methods. The non-endoscopic, less invasive methods, include the serologic tests, the labeled urea breath test and the monoclonal antibody-based *Helicobacter pylori* stool antigen test. The endoscopic tests, performed in the biopsy specimens obtained by upper endoscopy, are the rapid urease test, histopathology and culture[13]. The standard treatment to eradicate the *Helicobacter pylori* consists of a triple regimen of medications (a proton pump inhibitor, amoxicillin and clarithromycin, from 7 to 14 days), with eradication rates ranging from 70 to 80%[14]. Relapses can occur following the treatment, mainly in developing countries in comparison with developed countries, with relapse rates of 12 and 1.5%, respectively[15]. When recurrence develops one year or more after the treatment, it seems to be related to a new infection rather than to the reactivation of the prior infection[15].

Several pathophysiologic mechanisms have been suggested to explain the association between ChU and *Helicobacter pylori*. First, an IgE mediated immune response to the bacterial infection, since the patients with higher IgE levels on diagnosis show a more significant improvement of the symptoms of ChU in response to treatment institution[5]. Second, the release of auto-antibodies induced by the immunogenic bacterial cell wall[1,2], whose molecule is similar to the thyroid antiperoxidase antibody[16]. Finally, the presence of the *Helicobacter pylori* in the gastric mucosa stimulates the activated eosinophils to release cytotoxic proteins, which are involved in the pathophysiology of urticaria, and interfere with the production of pro-inflammatory cytokines and with the expression of

epitopes of adhesion to the endothelial cells, which triggers a systemic immune response[5]. Also, substances produced by the *Helicobacter pylori*, such as urease, protease, phospholipase and cytokines, can trigger the complement response[3].

The objective of this article is to report a case of ChU in a female adolescent that suggest a strong causal association with the infection by *Helicobacter pylori,* which was confirmed in two different occasions and showed improvement of the symptoms after treatment. The publication of this case report was approved by the Committee of Ethics on Research of the Universidade Federal de Pernambuco (UFPE).

Case report

A 13 year old female adolescent sought medical treatment at the Allergy and Immunology department of the Hospital das Clínicas da UFPE (HC-UFPE) for a complaint of urticarial lesions for one month. She had used 5 mg/day loradatine for seven days, and was under use of 40 mg/day prednisone for over 15 days, with mild clinical improvement. Her prior history included a mild intermittent allergic rhinitis, a history of asthma when school aged, and epigastric pain with the sensation of burning and gastric fullness for the last two months, which showed improvement with the use of 20 mg/day omeprazole. Her mother reported to be asthmatic and allergic to dypirone. The physical examination revealed urticarial lesions in the trunk and torso. The total blood cell count was normal, and total IgE was 272 UI/mL. In the following four months the patient received successive courses of treatment with 50mg/day hydroxyzine, 50mg/day desloratadine and 300mg/day ranitidine, followed by a 5 day course of treatment with 50mg hydroxyzine, 5mg desloratidine, and 40 mg prednisone daily, without any significant improvement. Further, courses of 10mg/day montelucaste and 10mg/day rupatadine were used as monotherapy in substitution to the other drugs, with no improvement of the symptoms.

An extensive etiological investigation was conducted. The blood cell count, biochemical, renal, hepatic and thyroid function tests, thorax and sinus X-Rays, abdominal ultrasound, urinalysis, and urine culture resulted normal. The cultures of the oropharingeal and vaginal secretions grew usual bacterial flora. The anti-thyroglobulin and anti-peroxidase antibodies were not detectable. The nontreponemal serologic screening (VDRL) and serologic tests for *Toxoplasma gondii*, rubella and cytomegalovirus showed positive IgG, but negative IgM reaction. The determinations of the serum immunoglobulines IgA, IgE, IgG and IgM and complement were also normal. The psychological evaluation of the adolescent and her mother revealed no behavioral or mood abnormalities.

Because the patient did not show any improvement of the urticaria and reported progressive worsening of the gastrointestinal symptoms, an upper endoscopy and investigation for *Helicobacter pylori* was performed. The gastric biopsy revealed moderate active chronic gastritis and the presence of *Helicobacter pylori*. Treatment with amoxicillin (2g/day), clarithromycin (1g/day) and omeprazole (40mg/day) for seven days was instituted, and rupatadine was maintained for more seven days. After 25 days, when the patient was off the anti-histamines, with resolution of the gastrointestinal symptoms and the urticarial were mild, occasional and transient, an autologous serum skin test was done and resulted non-reactive. The urticarial lesions became progressively sparser and eventually disappeared. A new upper endoscopy, performed nine months later, revealed normal gastric mucosa and the biopsy investigation for *Helicobacter pylori* was negative.

In 2011, at the age of nineteen, the patient sought the Allergy and Immunology Clinic of HC-UFPE reporting the urticarial lesions and epigastric pain to have relapsed two months earlier. She was taking 180mg/day fexofenadine, without symptoms relief. A new set of tests for investigation of the ChU was taken, all of which resulted normal: blood cell count, biochemistry tests, renal, hepatic and thyroid functions tests, urinalysis, anti-thyroglobulin and anti-peroxidase antibodies were not detectable. Serum Immunoglobulines A and M and complement levels were within the normal limits. Serologic tests for *Toxoplasma gondii* and cytomegalovirus resulted positive for IgG, but negative for IgM. Anti-HIV and VDRL serologic tests and stool testing were negative. Antinuclear antibodies and rheumatoid factor were undetected. Because of the current and past history, a new upper endoscopy was performed, and despite the normal macroscopic aspect of the gastric mucosa, the urease test resulted positive, confirming the reinfection by *Helicobacter pylori*. A new course of treatment with amoxicillin (2g/day), clarithromycin (1g/day) and omeprazole (40mg/day) for seven days was instituted, resulting in the total remission of the epigastric pain and of the ChU.

Discussion

ChU is a disease of complex ethiopathogenesis, in which multiple immunological and/or inflammatory mechanisms are involved, as well as several triggering and exacerbating factors, among which the infections play an important role. The case reported herein suggests a strong causal correlation between the *Helicobacter pylori* infection and the development of ChU, reinforced by the total remission of the symptoms of ChU when the proper antibiotic treatment was instituted, both in the first episode as in the reinfection.

To establish the etiological diagnosis of ChU is not an easy task and, according to Ferrer[6], in up to 75% of the patients undergoing an extensive investigation the etiology of the ChU cannot be determined, and they are classified as having spontaneous ChU. Due to the high frequency of the disease in the outpatients' clinics and emergency departments, in addition to its impact on the patients' quality of life, ChU must be investigated with detailed anamnesis and physical examination, in association with ancillary tests specifically driven according to the clinical history.

Growing evidence of the involvement of *Helicobacter pylori* in different extra intestinal conditions, among them the ChU, have been accumulated in the last years, and taking into consideration its high prevalence in developing countries, the investigation of *Helicobacter pylori* infection seems to be justified in patients with ChU with no established etiology, even for those with no gastrointestinal symptoms, as reported by Sackensen *et al*[17]. In the present report, because of the history of epigastric pain, the extensive laboratory investigation failing to detect the etiology of the ChU and the persistence of the urticarial lesions, an upper endoscopy was performed, which showed gastritis in association with *Helicobacter pylori.* The institution of specific treatment resulted in the remission of the symptoms.

The relationship between the infection by *Helicobacter pylori* with ChU has been the subject of discussion for many years, with controversial conclusions. In 2009, Wedi *et al*[3] reported the benefits of the eradication of this bacteria in patients with ChU in 13 studies (including a total of 322 patients), against 9 studies (164 patients) showing no benefits. In the studies that demonstrated the treatment to be beneficial, 84% of the patients showed either significant improvement or complete remission of the ChU after the bacterial eradication, in contrast with 45% of the patients who were infected but not treated, and 29% of the noninfected and not treated patients. When all the studies (with and without benefit) were analyzed, the rate of remission of the ChU after the treatment of the *Helicobacter pylori* was 61.5%, in comparison with 33.6% of the patients in which the bacteria was not eradicated, and 29.7% of the noninfected and not treated patients, which was statistically significant ($p<0.001$).

In 2010, Shakouru *et al*[10] evaluated 19 studies, 17 observational and 2 double blinded, randomized, controlled clinical trials, and showed that 10 of these studies showed a beneficial impact of the bacterial eradication in the resolution of the symptoms of ChU. The observational nature of the studies, the small number of patients and the short term follow up did not allow the drawing of definitive conclusions, resulting in low evidence for recommendation of the treatment. The etiologic investigation of the patients with different forms of urticaria showed that 3 of the 17 patients with ChU who had no gastrointestinal symptoms were positive for *Helicobacter pylori*. One of these patients, a 13 year old male adolescent, showed resolution of the ChU after eradication of the bacteria[17].

Therefore, despite controversial, the infection by Helicobacter pylori must be bared in mind in the investigation of patients with ChU, especially in those with upper gastrointestinal symptoms, once the treatment for eradication of this bacterium can lead to the relief of the symptoms and, consequently, the improvement of the patients' quality of life. Nevertheless, double blinded, controlled clinical trials with a larger number of patients and long term follow up are necessary to elucidate the actual role of this bacterium in the etiology of ChU.

References

1. Kanani A, Schellenberg R, Warrington R. Urticaria and angioedema. Allergy Asthma Clin Immunol 2011;7 (Suppl 1):S9.
2. Powell RJ, Du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT *et al*. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy 2007;37:631-50.
3. Wedi B, Raap U, Wieczorek D, Kapp A. Urticaria and infections. Allergy Asthma Clin Immunol 2009;5:10.
4. Zuberbier T. Chronic urticaria. Curr Allergy Asthma Rep 2012;12:267-72.
5. Castillo Reguera YM, Remón García C, Cabanillas Platero M, Cimbollek S, Díaz Flores I. Helicobacter pylori infection; a rarely suspected and treatable cause of chronic urticaria. An Pediatr (Barc) 2012;76:240-1.
6. Ferrer M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. Alergológica 2005. J Investig Allergol Clin Immunol 2009;19 (Suppl 2):21-6.
7. Calamita Z, Da Silva LA, França AC, Dias SM, Payão SL, Sperança MA. Comparative clinical study of Helicobacter pylori seroprevalence in patients with chronic urticarial from Marília – São Paulo (Brazil). Rev Bras Alerg Imunopatol 2003;26:146-51.
8. Ben Mahmoud L, Ghozzi H, Hakim A, Sahnoun Z, Zeghal K. Helicobacter pylori associated with chronic urticaria. J Infect Dev Ctries 2011;5:596-8.
9. Tüzün Y, Keskin S, Kote E. The role of helicobacter pylori infection in skin diseases: facts and controversies. Clin Dermatol 2010;28:478-82.
10. Shakouri A, Compalati E, Lang DM, Khan DA. Effectiveness of Helicobacter pylori eradication in chronic urticaria: evidence-based analysis using the grading of recommendations assessment, development, and evaluation system. Curr Opin Allergy Clin Immunol 2010;10:362-9.
11. Sebekina OV, Trubitsyna IE, Masharova AA, D'iakova EN. Clinical variants of chronic urticaria associated with helicobacter pylori. Exsp Klin Gastroenterol 2011;5:20-5.
12. Muller LB, Fagundes RB, Moraes CC, Rampazzo A. Prevalência da infecção por Helicobacter pylori e das lesões precursoras do câncer gástrico em pacientes dispépticos. Arq Gastroenterol 2007;44:93-8.
13. McColl KE. Helicobacter pylori infection. N Engl J Med 2010;362:1597-604.
14. Selgrad M, Malfertheiner P. Treatment of helicobacter pylori. Curr Opin Gastroenterol 2011;27:565-70.
15. Niv Y, Hazazi R. Helicobacter pylori recurrence in developed and developing countries: meta-analysis of 13C-urea breath test follow-up after eradication. Helicobacter 2008;13:56-61.
16. Kilic G, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. Pediatr Allergy Immunol 2010;21:837-42.
17. Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. Pediatr Dermatol 2004;21:102-8.

Rev Paul Pediatr 2013;31(2):272-5

No artigo: BRUSCKY, Dayanne Melo V.; ROCHA, Luiz Alexandre R. da; COSTA, Aldo José F.. Recurrence of chronic urticaria caused by reinfection by Helicobacter pylori. Rev. paul. pediatr. São Paulo , v. 31, n. 2, jun. 2013. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-05822013000200021&lng=pt&nrm=iso>. Acessos em: 20 mar. 2014. http://dx.doi.org/10.1590/S0103-05822013000200021.

Onde se lê: Dayanne Melo V

Leia-se: Dayanne Mota V