

Features of Antihistamine-Resistant Chronic Urticaria and Chronic Urticaria During Exacerbation

[Zhu Huilan](#), [Liang Bihua](#), [Li Runxiang](#), [Li Jiayan](#), [Lin Luyang](#), and [Li Zhenjie](#)

From the Department of Dermatology, Guangzhou Institute of Dermatology, Guangzhou, Guangdong, China. E-mail: zhluilan@hotmail.com

Copyright : © Indian Journal of Dermatology

This is an open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Sir,

In clinic, the treatment of chronic urticaria (CU) commonly presents some challenges for the dermatologist. Antihistamines are the first-line treatment in CU,^[1] but sometimes CU is resistant to it, even high doses. In another side, urticaria is a skin disease characterized by short-lived wheals and we all know that the wheals in CU can fade by themselves. What are the differences between antihistamines-sensitive CU and antihistamines-resistant CU and what are the differences during CU exacerbation and during remission? To study these maybe good for further understanding the pathogenesis of CU.

In our study, the plasma levels of prothrombin fragment 1 + 2 (F1 + 2), tissue factor (TF), thrombomodulin (TM), high molecular weight kininogen (HMWK), tissue-type plasminogen activator (t-PA), C5a, C3, C4, antistreptolysin O (ASO), rheumatoid factors (RF), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were determined in CU patients (17 antihistamines-sensitive CU and 23 antihistamines-resistant CU; 22 during CU exacerbation and 18 during remission). Urticaria activity score and autologous serum skin test (ASST) were also assessed.

Plasma concentration of F1 + 2 in exacerbation CU patients (985.36 ± 285.77 pmol/L) were significantly higher than those in remission CU patients (579.40 ± 305.87 pmol/L) ($P < 0.01$). However there was no significant difference of plasma levels of TF, TM, HMWK, t-PA, C5a and serum levels of C3, C4, ASO, RF, CRP and ESR between exacerbation CU patients and remission CU patients ($P > 0.05$) [Figures 1 and 2]. Plasma levels of C5a were higher in antihistamines-resistant CU patients (50.67 ± 16.83 pmol/L) than those in antihistamines-sensitive CU patients (40.43 ± 10.89 pmol/L) ($P < 0.05$), but there was no statistical difference in plasma levels of F1 + 2, TF, TM, HMWK, t-PA and serum levels of C3, C4, ASO, RF, CRP and ESR between them ($P > 0.05$) [Figures 3 and 4]. In CU patients, antihistamines sensitive/antihistamines resistant was correlated with symptom scores and duration of wheals ($r = 0.42$, $P < 0.01$; $r = 0.57$, $P < 0.01$). In antihistamines-resistant CU patients, we found higher symptom scores and longer duration of wheals. However, antihistamines sensitive/antihistamines resistant was not correlated disease course ($r = 0.11$, $P > 0.05$) [Table 1]. Compared with antihistamines-sensitive CU patients, antihistamines-resistant CU patients was characterized with more positive ASST (12/23 in antihistamines-sensitive CU patients versus 15/17 in antihistamines-resistant CU patients; $P < 0.05$) [Table 2].

In this study, we found that plasma concentrations of F1 + 2 in CU patients during the exacerbation were significantly higher than those in remission patients ($P < 0.01$). We assume that the concentration of thrombin tends to recover as CU comes to remission gradually. This may give explanation for the phenomenon why the wheals in CU fade by themselves. In our former study, we found that antihistamine can act on coagulation as the levels of coagulant factors trend toward recovery after antihistamine administration.^[2] Studies have shown that thrombin participates in mast cell degranulation by activating protein kinase receptor on the mast cell surface.^[3] Solute permeability may result in cutis and mucosal

edema.[4] But this effect can be blocked by antihistamine drug administration or mast cell granule attenuation.[5] Antihistamine may play a key role in inhibiting the activation of coagulation cascade in CU.

We also observed that complement C5a concentration increased significantly in antihistamine-resistant patients. The resistance to antihistamine may be related to upregulation of plasma levels of C5a in CU patients. It has been demonstrated a new complement activation pathway that C5a generated in the absence of C3 by thrombin, which took place of C5 convertase in the classical pathway.[6] Pathogenic IgG cross-links the IgE receptor directly to cause histamine release, and the activation is augmented by complement. C5a is the complement agonist that is responsible for the augmented histamine release.[7] We also found the antihistamines-resistant CU patients with upregulation of plasma levels of C5a, higher activity scores, longer duration of wheals and more positive ASST. hence we considered that resistance to antihistamine in CU patients may be related to immunoreaction intervened by complement.

Conclusion

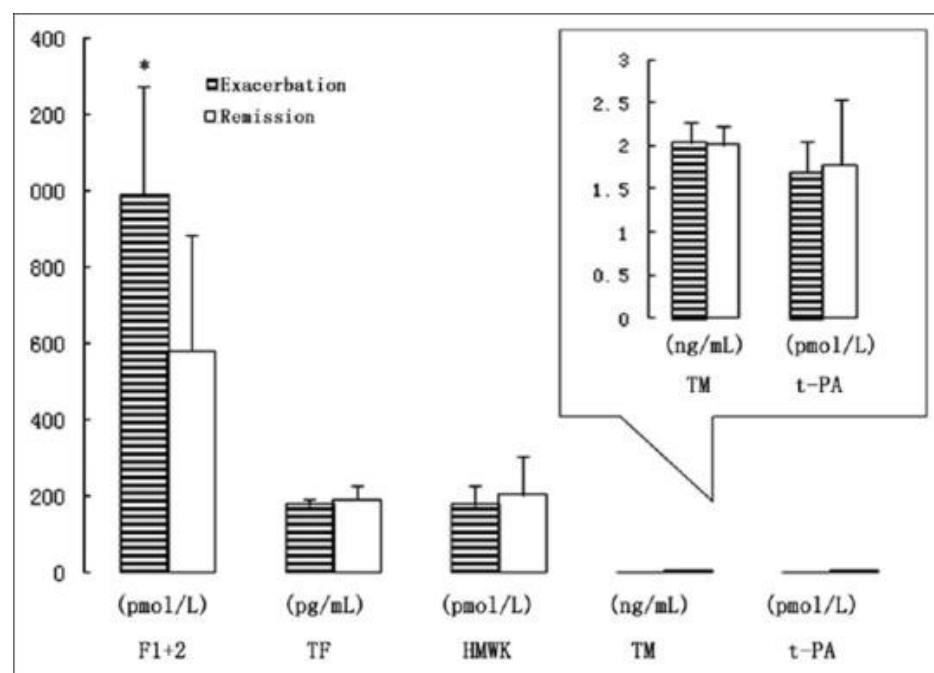
The resistance to antihistamine could be related to upregulation of plasma levels of C5a, higher activity scores, longer duration of wheals and more positive ASST, but not to those of coagulant and anticoagulant factors and fibrinolytic markers in CU patients; CU during the exacerbation and during remission maybe differ in coagulation.

References

1. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM, et al. EAACI/GA (2) LEN/EDF/WAO guideline: Management of urticaria. *Allergy*. 2009;64:1427–43. [PubMed: 19772513]
2. Zhu H, Liang B, Li R, Li J, Lin L, Ma S, et al. Activation of coagulation, anti-coagulation, fibrinolysis and the complement system in patients with urticaria. *Asian Pac J Allergy Immunol*. 2013;31:43–50. [PubMed: 23517393]
3. Kido H, Fukusen N, Katunuma N, Morita T, Iwanaga S. Trypsin from rat mast cells converts bovine prothrombin to thrombin. *Biochem Biophys Res Commun*. 1985;132:613–9. [PubMed: 3904753]
4. Schaeffer RC, Jr, Gong F, Bitrick MS, Jr, Smith TL. Thrombin and bradykinin initiate discrete endothelial solute permeability mechanisms. *Am J Physiol*. 1993;264:H1798–809. [PubMed: 8322908]
5. Cirino G, Cicala C, Bucci MR, Sorrentino L, Maraganore JM, Stone SR. Thrombin functions as an inflammatory mediator through activation of its receptor. *J Exp Med*. 1996;183:821–7. [PMCID: PMC2192352] [PubMed: 8642286]
6. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, et al. Generation of C5a in the absence of C3: A new complement activation pathway. *Nat Med*. 2006;12:682–7. [PubMed: 16715088]
7. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. *J Allergy Clin Immunol*. 2002;109:114–8. [PubMed: 11799375]

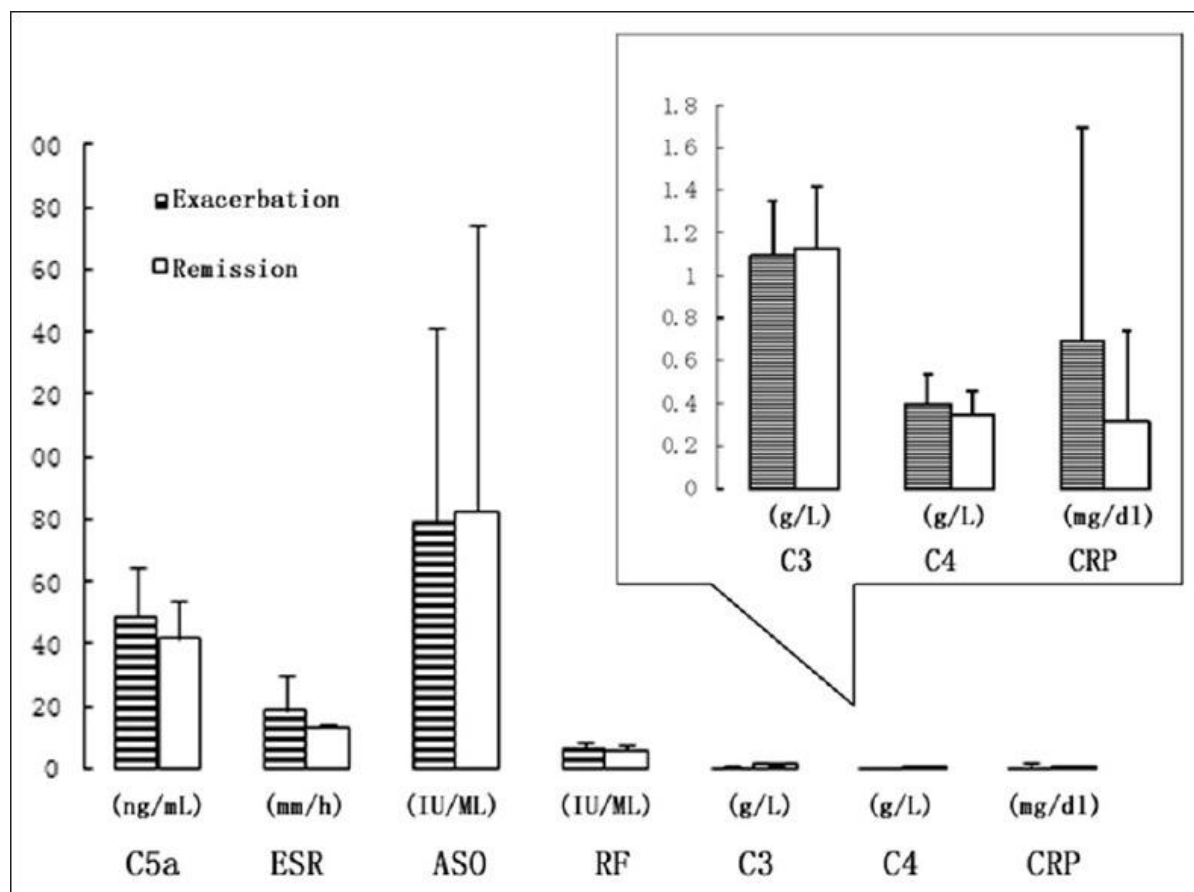
Figures and Tables

Figure 1



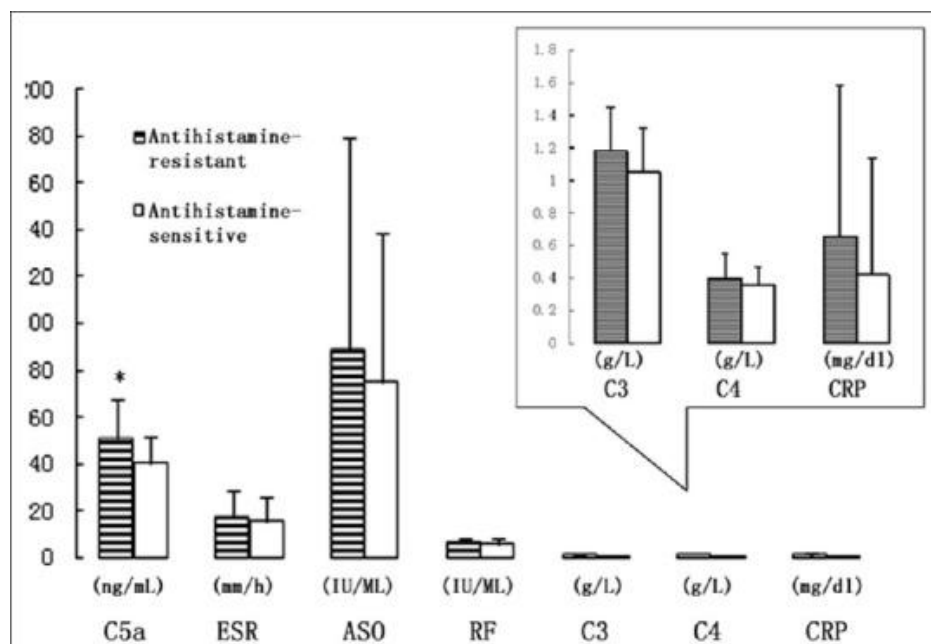
Plasma levels of F1 + 2, tissue factor, thrombomodulin, high molecular weight kininogen and tissue-type plasminogen activator in chronic urticaria patients during exacerbation and during remission (* $P < 0.01$)

Figure 2

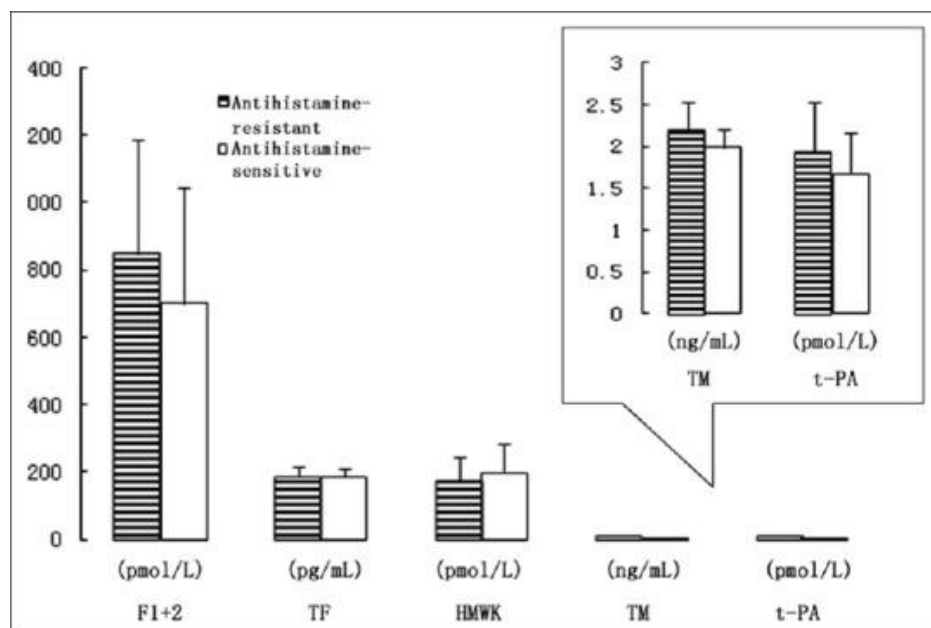


Plasma levels of C5a and serum levels of C3, C4, antistreptolysin O, rheumatoid factors, C-reactive protein and erythrocyte sedimentation rate in chronic urticaria patients during exacerbation and during remission ($P > 0.05$)

Figure 3



Plasma levels of C5a and serum levels of C3, C4, antistreptolysin O, rheumatoid factors, C-reactive protein and erythrocyte sedimentation rate in antihistamine-resistant and antihistamine-sensitive chronic urticaria patients (* $P < 0.05$)

Figure 4

Plasma levels of F1 + 2, tissue factor, thrombomodulin, high molecular weight kininogen and tissue-type plasminogen in antihistamine-resistant and antihistamine-sensitive chronic urticaria patients ($P > 0.05$)

Table 1

Subject	Course	Activity scores	Duration of wheals
Response to antihistamines			
<i>r</i>	0.11	0.42	0.57
<i>P</i>	0.52	<0.01	<0.01

CU: Chronic urticaria

Correlation with response to antihistamines in CU patients

Table 2

Subject	ASST (+)	ASST (-)	Total
Antihistamine-resistant CU	15	2	17
Antihistamine-sensitive CU	12	11	23
	27	13	40

$\chi^2=4.27$, $P<0.05$. ASST: Autologous serum skin test, CU: Chronic urticaria

Results of ASST in antihistamine-resistant and antihistamine-sensitive CU patients

Articles from Indian Journal of Dermatology are provided here courtesy of **Medknow Publications**