A simple, combined test using laboratory and clinical data, can improve the diagnosis of autoimmune urticaria

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Sir, the diagnosis of autoimmune chronic urticaria (AIU) is difficult. Autologous serum skin test (ASST) is a screening method to diagnose AIU and was first used by Grattan et al., and was standardized by Sabroe et al[1,2]. One major limitation of ASST is that positivity can refer not just to the presence of functional autoantibodies against FcεRIα or IgE, but other yet unidentified serum factors[2]. Besides the advantages of ASST which are its fast and easy implementation and its cost, since its positivity alone cannot define AIU, other methods are needed to confirm the diagnosis of AIU. Some study groups suggested immunoassay methods (immunoblot, ELISA) to detect autoantibodies[3], but these tests are time-consuming, cannot differentiate between functional and non-functional autoantibodies and may also yield false positive and negative results[2,4]. Functional tests such as basophil histamine release assay (BHRA) and basophil CD63 assay have the best sensitivity and specificity in the diagnosis of AIU[5,6]. However, both BHRA and basophil CD63 assay are difficult to perform, time-consuming, expensive and several laboratories do not have the conditions to use them which make these tests unsuitable for clinical practice. The aim of our study was to improve the diagnostic value of ASST by keeping the method but adding a combination of clinical/anamnestic and laboratory data to it.

55 chronic spontaneous urticaria (CSU) patients were selected. According to the guideline, patients whose urticarial symptoms suggested auto-inflammatory disease, urticarial vasculitis, chronic inducible urticaria, hereditary angioedema, or ACE-inhibitor induced angioedema were excluded from the study[7]. Antihistamine treatment was stopped at least 4 days before, and corticosteroid or immunosuppressive therapy at least 2 months before serum samples were collected for investigation and analysis. A detailed questionnaire was filled out by the patients to collect anamnestic/clinical data (listed in Table 1a). Laboratory tests [anti-thyroglobulin antibody (anti-TG), anti-thyroid peroxidase antibody (anti-TPO)] and ASST were also performed. When the study was initiated Breneman score was used to determine the severity of urticaria. With Breneman score the number of lesions, number of separate episodes, average size and duration of lesions, and pruritus can be rated from 0 to 3 with a maximum point of 15. Above 10 points was considered to be severe[8]. AIU was diagnosed according to the positivity of basophil CD63 assay[6] and laboratory and anamnestic/clinical data of AIU and non-AIU patients were compared by using Fisher's exact test. Significantly more frequently occurring laboratory and anamnestic/clinical data in the AIU group was considered as specific characteristics of AIU patients. Logistic regression model was used to decide which combination of ASST and these specific parameters could increase the sensitivity and specificity of the ASST in order to reach that of basophil CD63 assay.

All patients gave written informed consent, which was in accordance with the guiding principles for human experimentation summarized in the Declaration of Helsinki. The study was approved by the Local Ethics Committee.

19 men, 36 women were included in the study, mean age was 49.2 years (SD=15.15), mean duration of the disease was 18.4 months (SD=14.5). 33 CD63+ patients were diagnosed with AIU and 22 CD63- patients were diagnosed with chronic spontaneous non-AIU (Table 1a).

Those parameters which occurred significantly more frequently in the AIU group and was defined as specific to AIU, were the followings: the ASST positivity, the occurrence of symptoms at night, the occurrence of angioedema, more than 5 symptomatic days/week, and the anti-thyroid antibody positivity (Table 1a).

In the diagnosis of AIU, ASST alone had a sensitivity of 88% and a specificity of 77%. With the logistic regression method all the possible combinations of ASST and the specific parameters of AIU were evaluated to decide which combination has the highest sensitivity and specificity. If the ASST was combined with all the specific parameters, the best sensitivity (97%) and specificity (86%) values were reached (Table 1b).

According to the EAACI taskforce position paper the gold standard diagnostic steps in AIU are proposed to contain a bioassay (BHRA, basophil CD63 assay), the ASST, and an immunoassay (ELISA, immunoblot) together[9]. On the other hand, these tests are currently of limited use for everyday clinical practice. Gimenez-Arnau et al. suggests only limited number of routine diagnostic measures (blood count, level of ESR or CRP, omission of suspected drugs) in CSU and extended tests (e.g. ASST, detection of autoantibodies) are advised only to be done if the symptoms are severe and long-standing[7]. We believe that identifying the AIU group is essential. According to our experience AIU is severe and more therapy resistant compared to the non-AIU[10]. It would be worth adding the inexpensive and simple ASST to the routine test section with the combination of thyroid laboratory tests and anamnestic/clinical data to facilitate the diagnosis of AIU. This easy to use, combined test with excellent sensitivity and specificity can be used for the diagnosis of AIU in outpatient settings also.

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(a)

	CD63+ (%) n=33	CD63- (%) n=22	p value
age (year)	49.6 SD=16.2	48.5 SD=13.7	0.717
ASST positivity	**29 (87.9)**	**5 (22.7)**	**<0.001**
occurrence of angioedema	**27 (81.8)**	**6 (27.3)**	**<0.001**
occurrence of symptoms at night	**27 (81.8)**	**10 (45.5)**	**0.008**
>5 symptomatic days/week	**32 (97)**	**9(40.9)**	**<0.001**
anti-thyroid antibody positivity (anti-TG, anti-TPO)	**21 (63.6)**	**2 (9.1)**	**<0.001**
female	27 (81.8)	16 (72.7)	0.512
>6 months of duration of chronic urticaria	23 (69,7)	11 (50)	0,270
duration time of a wheal (5-24 hours)	28 (84.8)	15 (68.2)	0.188
high dose of antihistamine therapy	24 (72.7)	12 (54.5)	0.247
thyroid disease in the history	6 (18.2)	3 (13.6)	0.727
Breneman score (>10 points)	7 (21.2)	5 (22.7)	0.482
vitiligo	4 (12.1)	0	-
alopecia areata	0	0	-
other, than antihistamine therapies	16 (48.5)	0	-

(b)

ASST positivity	>5 symptomatic days/week	occurrence of angioedema	anti-thyroid antibody positivity	occurrence of symptoms at night	Sensitivity	Specificity	PPV%	NPV%
X	**X**				0.88	0.91	93.5	83.3
X		**X**			0.88	0.77	85.2	81
X			**X**		0.91	0.68	81.1	83.3
X				**X**	0.88	0.77	85.3	81
X	**X**	**X**			0.97	0.82	88.9	94.7
X	**X**	**X**	**X**		0.94	0.86	91.2	90.5
X	**X**	**X**	**X**	**X**	**0.97**	**0.86**	**91.4**	**95**

Table 1 (a) Comparison of clinical/anamnestic data and thyroid laboratory tests of AIU and non-AIU patients. Parameters which occurred significantly more frequently in the AIU group are listed with bold letters and considered as specific parameters **(**anti-TG: anti-thyroglobulin, anti-TPO: anti-thyroid peroxidase, high dose of antihistamine therapy: double or more dose of the licensed dose, other than antihistamine therapy: e.g. Cyclosporin A, plasmapheresis). Occurrence of vitiligo and other than antihistamine therapies in the history were found only in the AIU group therefore p value could not be calculated (b) Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ASST alone and the combination of ASST + 1 or more specific parameter(s)