Title: Detection of Adrenal insufficiency(AI) in severe and moderate asthma

30.00

25.00

20.00

5.00

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Basic Data: diurnal variation of CS

4.82

Basic Data: ACTH Prov-Test

Cortisol level after ACTH

─ A

1.69

1.44

2.47

··• AB

Diurnal variation of CS

$1 \Rightarrow Summary$

Systemic corticosteroid (CS) is necessary for control of asthma in moderate to severe asthma although they often result in adrenal insufficiency(AI) that need hydrocortisone (cortisol, Cortoril®) replacement therapy. We attempted to describe characteristics of those with possible AI in order to detect those who might need replacement therapy.

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METHODS: One hundred twenty eight patients agreed to participate in assessment of AI by tests including:(1)Diurnal cortisol sampling(DiCS) at 6:00, 11:00,15:00,23:00; (2)ACTH provocation test (3) 24 urinary cortisol Nine out of 21(42.9%) were treated with biologics for severe steroid dependent asthma and displayed symptoms of AI after reduction or discontinuation of systemic CS. In some, use of systemic CS for other purpose seemed to have induced AI, together with asthma-like symptoms, ie, treatment for lymphoma with high dose OCS(FM,F,48yo), receiving triamcinolone for lumber pain(NS,M,69yo) (ER,F, 36yo), all of which developed asthma-like symptoms and were treated as asthma a some point. Others with AI had EGPA (KM,M, 35yo), chemical hypersensitivity

syndrome(IM, F, 46yo). They recovered after replacement therapy with hydrocortisone. Those with AI had past history of high dose steroid (p<0.0000), early onset of asthma(p<(0.0377), higher frequency of acute exacerbation (p<0.0055), history of sinusitis(p<0.0009), hospital admission (p<0.0368), higher rate of biologic use(p<0.0136) and passive smoking (p<000). They also had tendency experiencing remission(p<0.055) and recurrence(p<0.083), chemical hypersensitivity(p<0.08), slightly higher nervousness measured by CMI(p<0.096), but less depression, measured by CES-D(p<0.069), and their staturence (p<0.069).

tended to be higher (p<0.081).

CONCLUSION: Those with severe asthma may acquire better control if they are assessed properly and treated for their underlying AI.

2 > Rationale

Severe asthma with adrenal insufficiency (AI) is difficult to diagnose withou index of suspicion due to their non-specific symptoms.

Typical symptoms for AI:

(1) Indefinite symptoms: unidentified fatigue, dyspnea, headache, diarrhea, malaise, weakness in the morning, daytime somnolence, recurrent infections, muscle cramp, chronic cough, loss of interest, arthralgia, etc.

(2) Syncope: Sudden loss of consciousness, hypotension, palpitation, arrhythmias, vertigo, tinnitus, dyspnea, chest tightness, etc.

(3) <u>Depression and/or anxiety</u>: sleep disturbance, irritability, apathy, etc. (4) Steroid Dependency: Taking oral steroid from anxiety rather than by objective sign of asthma exacerbation.

■ Importance of defining AI in asthma:

(1)Possible early action for severe asthma and suddensituation such as anaphylaxis as part of adrenal crisis(A/C) if underlying AI is well characterized at early stage.

(2) May avoid repeated asthma symptoms part of which may arise from AI/low adrenal function as their primary problem.

(3) Replacement therapy: Physiological dose of hydrocortisone may support well being of each patient.

In this study we attempted to define AI in asthma:

Asthma patients with severe AI (Group A),pre-AI(group B),borderline AI(Group C) and near normal(Group D) was

analyzed for comparison.

Profiles of Patients:

| Sev | erity of adrenal | Male | | Female | | Total |
|------------|------------------------------|------|-------|--------|-------|-------|
| iı | nsufficiency (AI) | No. | % | No. | % | Iutai |
| Group A | Severe AI n=21 | 8 | 38.1% | 13 | 61.9% | 21 |
| Group B | Moderate to Severe AI n=50 | 13 | 26.0% | 37 | 74.0% | 50 |
| Group C | Moderate AI n=18 | 5 | 27.8% | 13 | 72.2% | 18 |
| Group D | Mild AI n=39 | 13 | 33.3% | 26 | 66.7% | 39 |
| Total | Total | 39 | 30.5% | 89 | 69.5% | 128 |
| B + C + D | Group other than A n=107 | 31 | 29.0% | 76 | 71.0% | 107 |
| B + C | Moderate to severe n = 68 | 18 | 26.5% | 50 | 73.5% | 68 |

[1]Patient group designated according to their level of severity.

[2] AI assessment: ACTH provocation test: cortisol level at

0', 30',60 min: Diurnal cortisol: sampling: 6,11,15,23hr,2days: 24 urinary cortisol concentration/day, 2days

[3] Criteria for group A~D:

 $3 \Rightarrow Method$

■Group A (N=21)(16.4%): Severe AI, minimal recovery expected: DiCS: Peak cortisol less than 5 µg/dl at all points(N=21,100%) ACTH Pro-Test: Peak cortisol less than 25µg/dl (N=21,100%)

24 hr UC: normal 1/21(N=1/4.8%), abnormal 20/21 (N=20,95.7%)

Group B (N=50): Moderate /severe AI, poor recovery expected:

DiCS: Peak cortisol over 5 μg/dl at least at one point (N=50,100%)

ACTH Pro-Test: Peak cortisol, less than 25µg/dl(N=50,100%)
24hr UC: normal 37/50(N=37,74%); abnormal 13/50 (N=13,26%)

Group C (N=18): Moderate AI, high chance of recovery:

DiCS: Peak cortisol over 5 μg/dl at least at one point (N=18,100%) ACTH Pro-Test:Peak cortisol, more than 25μg/dl (N=18,100%) 24 hr UC: below normal in 3 /18 persons.(N=3, 16.7%)

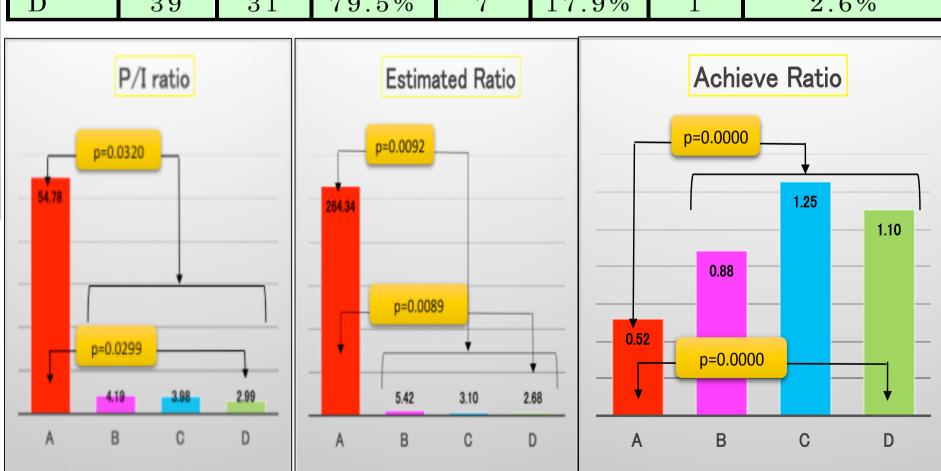
Group D(N=39): Near normal AI:DiCS: Peak cortisol over 5 μg/dl at 6am, 11am, 16pm(N=39,100%)2hr UC: within normal range (N=39,100%). ACTH Pro-Test, Peak cortisol, more than 25μg/dl; 25/39(N=25,64.1%), less than 25μg/dl; 14 / 39 (N=14,35.8%),5 / 39(N=25,64.1%)

PS: Gr AB: higher risk for AI, Gr CD: lower risk for AI; Gr ABC: moderate to severe AI, Gr BCD: mild to moderate AI.

Each Group Compared with Normal Rapid ACTH Test in Phase I Studies to obtain achieve ratio(AR)

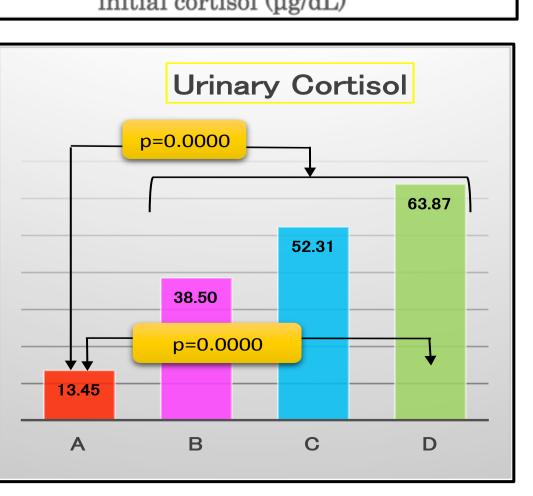
Initial(I) and peak(P) cortisol level and P/I Ratio was obtained in groups A~D by rapid ACTH test. Data compared with predicted estimate ratio(ER)for healthy controls and expressed as achieved ratio(AR) to evaluate the level of adrenal insufficiency in each of the group of patients compared to the healthy controls.

| AR(arc | hive ra | | | | | | | | | |
|--------------|---------|--------|--------|----------------------|-------|--------|-------|--|--|--|
| Group | Total | AR>1.0 | | $1.0 \ge AR \ge 0.5$ | | AR<0.5 | | | | |
| | | No. | % | No | % | No | % | | | |
| A | 21 | 1 | 4.8% | 9 | 42.9% | 11 | 52.4% | | | |
| В | 50 | 13 | 26.0% | 35 | 70.0% | 2 | 4.0% | | | |
| \mathbf{C} | 18 | 18 | 100.0% | 0 | 0.0% | 0 | 0.0% | | | |
| D | 39 | 31 | 79.5% | 7 | 17.9% | 1 | 2.6% | | | |
| | | | | | | | | | | |



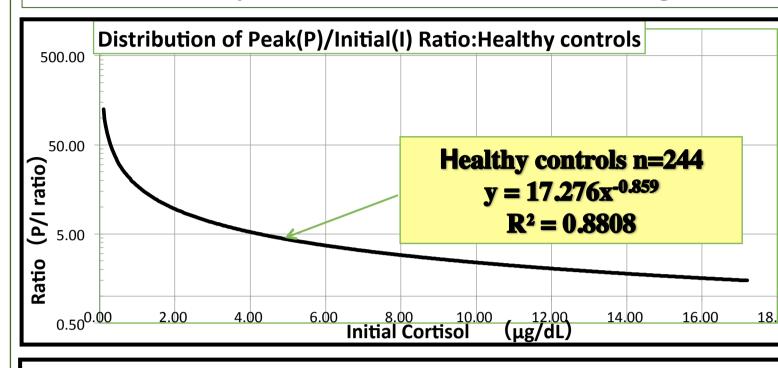
Standard curve for rapid ACTH test was reported previously by our co-author and was employed for this study [Jpn J Clin Pharmacol Ther 31(4) July 2000]. This was done under co-operation of 244 healthy normal controls(N=244,SD=0.1235).

Compared to the normal control group, Group A with severe adrenal insufficiency, Achieved ratio(AR) above 1.0 was only 4.8%, while the AR for Group B was 26.0%. Group C and Group D with near normal profiles had higher percentage of those with AR above 1.0, in other words, in Group C, the percentage of AR above 1.0 was100, while Group D had 79.5%, respectively. Peak and the Initial cortisol ratio=P/I was employed to compared to obtain achieved ratio, P/I plotted for each group against initial cortisol displayed the level of cortisol in comparison with the curve obtained from the healthy control group which may also be expressed as "a standard curve" for adrenal function. Those below the standard curve may be judged as having poor adrenal function(group A,B) while those above may be said to have normal or near normal function(Group C,D). This standard curve may be used to express individual vale as well as for evaluating certain group of patients under examination.

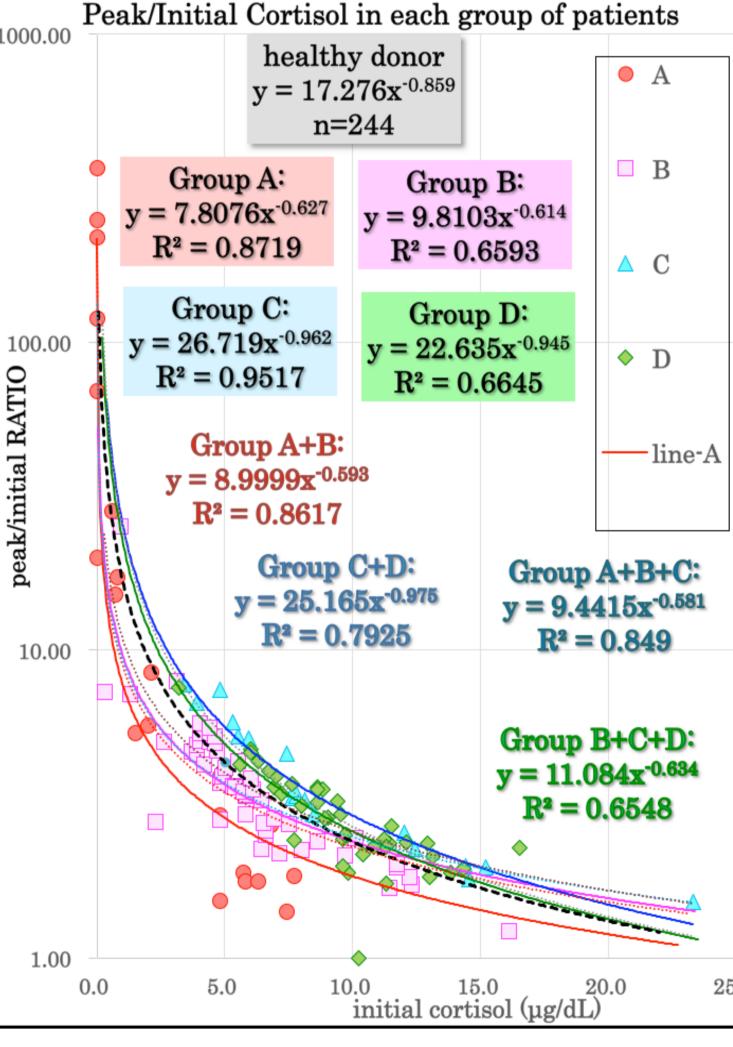


Made under co-operation of 244 healthy normal control patients (N=244, SD=0.1235) (Jpn J Clin Pharmacol Ther 31 (4) (July 2000) were employed to compare each AI group. Initial (I) and peak (P) cortisol level were obtained to see P/I Ratio from each group of patients undergoing rapid ACTH test. P/I ratio for normal healthy individual was designated as Z1/Z0 while P/I ratio for asthma patients were designated Y1/Y0 (Figure below.) Abnormal reactivity pattern was detected by comparing Y1 and Z1, supposing that the value should be Y1/Z1=1 if the cortisol reaction by ACTH stimulation were normal. (Figure 1)

4 >> Standard curve for rapid ACTH test to obtain AR:



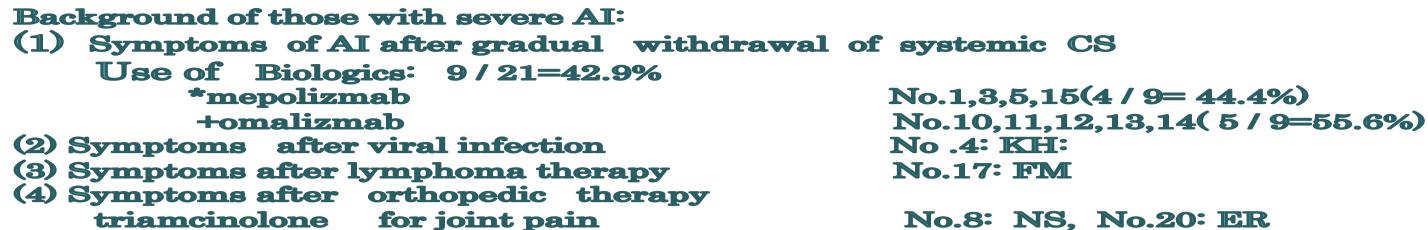
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Grouping into A,B,C,D was done according to definition above. Each group discriminated well from each other except for C,D,both being near normal. B and C had similar diurnal curve for cortisol but were differentiated by response to ACTH Provocation test(above).

■24 hour urinary cortisol level was correlated well according to the expected level of adrenal function.

[A] Twenty-one patients (16.4%) with severe AI:



(5) EGPA(with asthma)
(6) Chemical hypersensitivity
(7) ACTH depletion
(8) Long history of severe asthma since childhood

NO5: KS; No10:SE; No.13:MR;
No 14; NN; No 15:UM

(9) E NT infection :

NO5: KS; No10:SE; No.13:MR;
No 14; NN; No 15:UM

These patients were treated with physiological dose of hydrocortisone (Cortril ®)according to their body weight and are gradually recovering from non-specific and indefinite Symptoms of adrenal insufficiency and also have not experienced any major asthma symptoms regardless of the fact that they were classified to have very severe asthma.

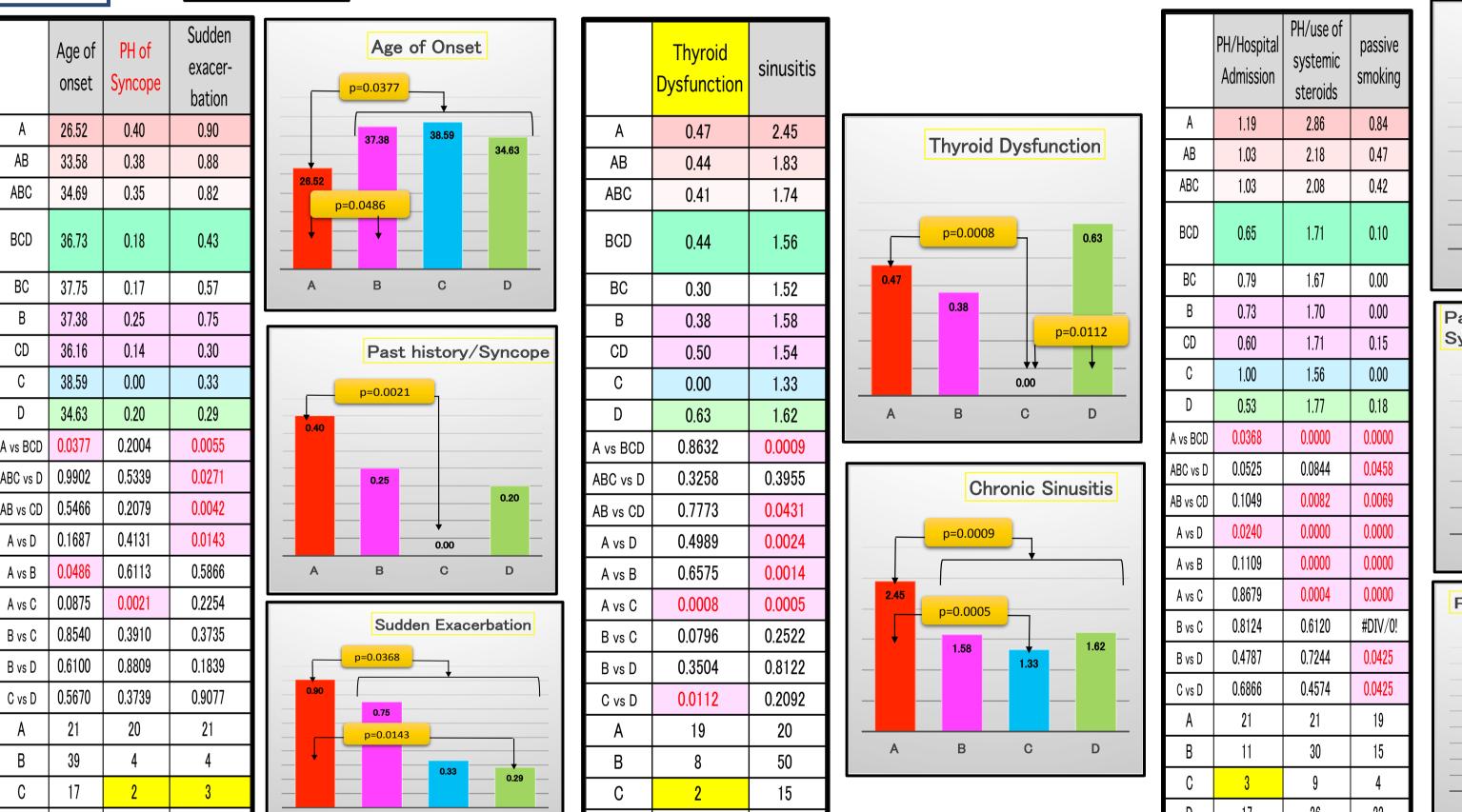
No1;OK, No2.:OY;No16:SK,No21:NN

Past history/

7-2 Result-2 [B] Characteristic of

(10)Occupational stress:

[B] Characteristic of group A patients compared to other groups.





■Those with severe adrenal insufficiency/adrenal crisis(AI/AC) may not be apparent due to their unspecific nature and may appear only after certain stressful conditions. Although AI/AC is difficult to diagnose in a definite manner at present though evaluation at early stage is desirable since some may need prompt care in case of emergencies and is better if prevented beforehand.

■We hope Peak and Initial ratio of rapid ACTH test could be an efficient index to detect secondary adrenal insufficiency which is feasible in daily clinical setting.

■Early suspicion and replacement therapy with hydrocortisone could be life saving for severe cases of adrenal insufficiency(AI) including adrenal crisis (AC).

■It is advisable that all patients be diagnosed for possible AI/AC and should carry an Emergency Card to ensure best care for AI.

9 > Summary and conclusion

Not many clinician evaluate AI on routine bases and give necessary treatment. Evaluation of adrenal function will enable clinician to treat AI with hydrocortisone which is more native to human hormone and may improve the control and prevent recurrence through more natural mechanism. Other results displayed relation with thyroid function and passive smoking.

Former may be due to similar endocrinological nature of the patient while passive smoking may be related to increase in eosinophil and other nature related to chemical hypersensitivity which may be inter-related to each other. Replacing the natural human hydrocortisone and has only minimal side-effect and low in cost compared to present standard asthma medication. We should at least take a more close look to this area and find adequate patients with indication for hydrocortisone replacement therapy.