

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

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1 → 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, Cortril®) replacement therapy. We attempted to describe characteristics of those with possible AI in order to detect those who might need replacement therapy.

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(FMF,48yo), receiving triamcinolone for lumbar pain(NS,M,39yo) (ER,F,36yo), all of which developed asthma-like symptoms and were treated as asthma at 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<0.00001),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<0.00).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 stature 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 without 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) **Depression and/or anxiety:** 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 sudden situation 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:

Severity of adrenal insufficiency (AI)	Male		Female		Total
	No.	%	No.	%	
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	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

3 → Method

[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:

Group A (N=21)(16.4%): Severe AI, minimal recovery expected: DiCS: Peak cortisol less than 5 μ g/dl at all points(N=21,100%) ACTH Pro-Test: Peak cortisol less than 25 μ g/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 μ g/dl at least at one point (N=50,100%) ACTH Pro-Test : Peak cortisol, less than 25 μ g/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 μ g/dl at least at one point (N=18,100%) ACTH Pro-Test:Peak cortisol, more than 25 μ g/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 μ g/dl at 6am, 11am, 16pm(N=39,100%)2hr UC: within normal range (N=39,100%). ACTH Pro-Test, Peak cortisol,more than 25 μ g/dl ; 25/39(N=25,64.1%), less than 25 μ g/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.

5 → 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(archive ratio) of each group

Group	Total	AR > 1.0		1.0 ≥ AR ≥ 0.5		AR < 0.5	
		No.	%	No.	%	No.	%
A	21	1	4.8%	9	42.9%	11	52.4%
B	50	13	26.0%	35	70.0%	2	4.0%
C	18	18	100.0%	0	0.0%	0	0.0%
D	39	31	79.5%	7	17.9%	1	2.6%

Group A+B: y = 8.9999x^{-0.598} R² = 0.8617

Group C+D: y = 26.719x^{-0.962} R² = 0.9517

Group A+B+C: y = 25.165x^{-0.976} R² = 0.7925

Group B+C+D: y = 11.084x^{-0.634} R² = 0.6548

P/I ratio

Estimated Ratio

Achieve Ratio

p=0.0320

p=0.0092

p=0.0000

p=0.0299

p=0.0089

p=0.0000

p=0.0000

p=0.0000

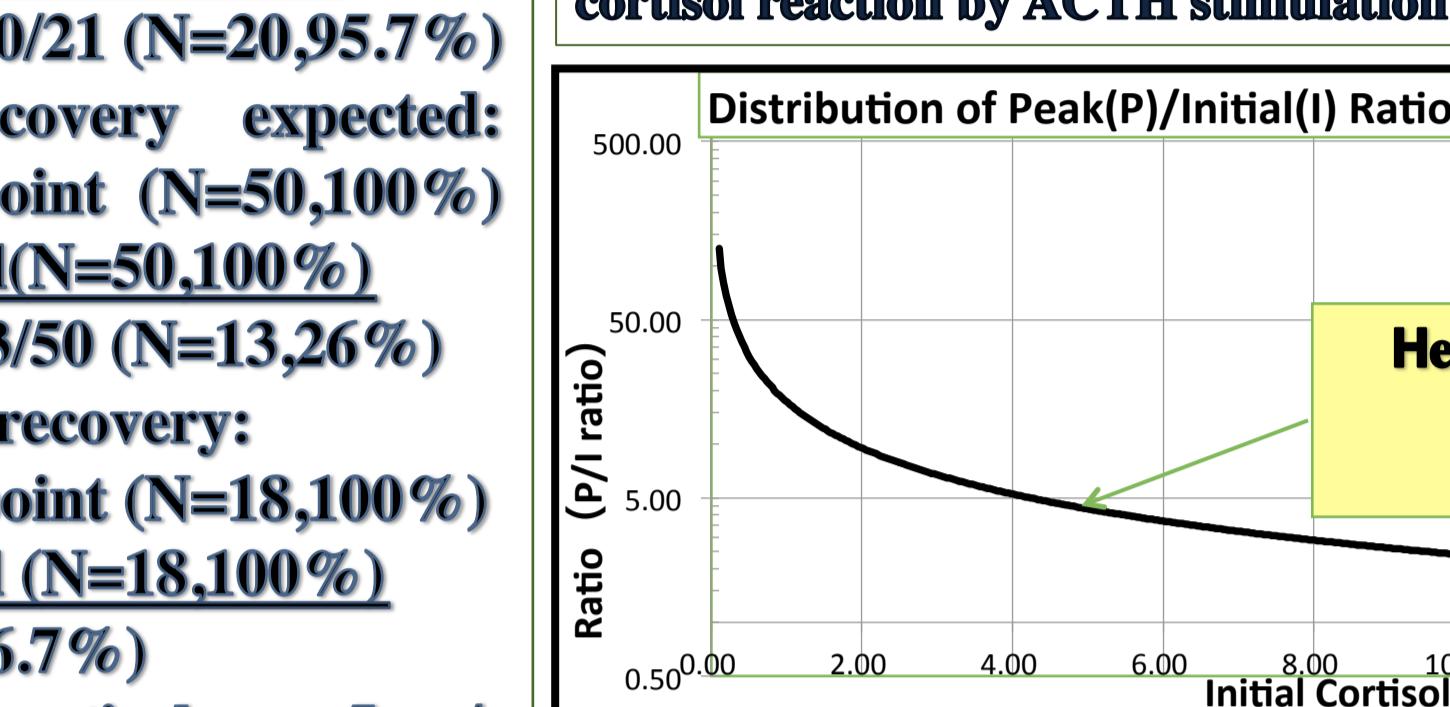
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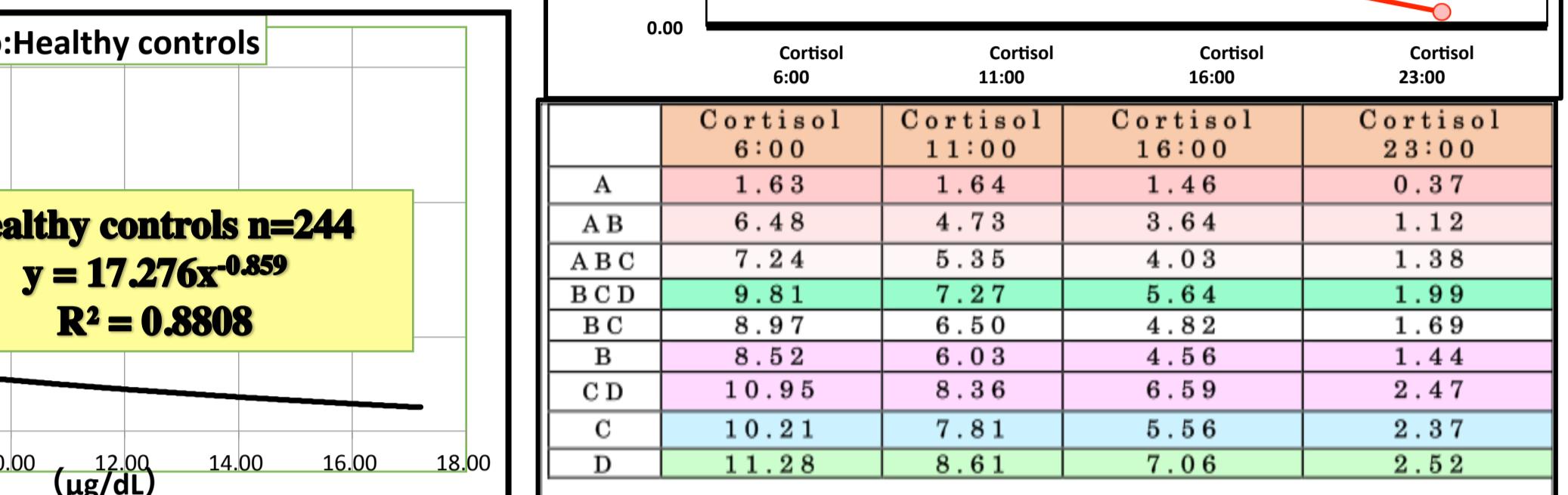
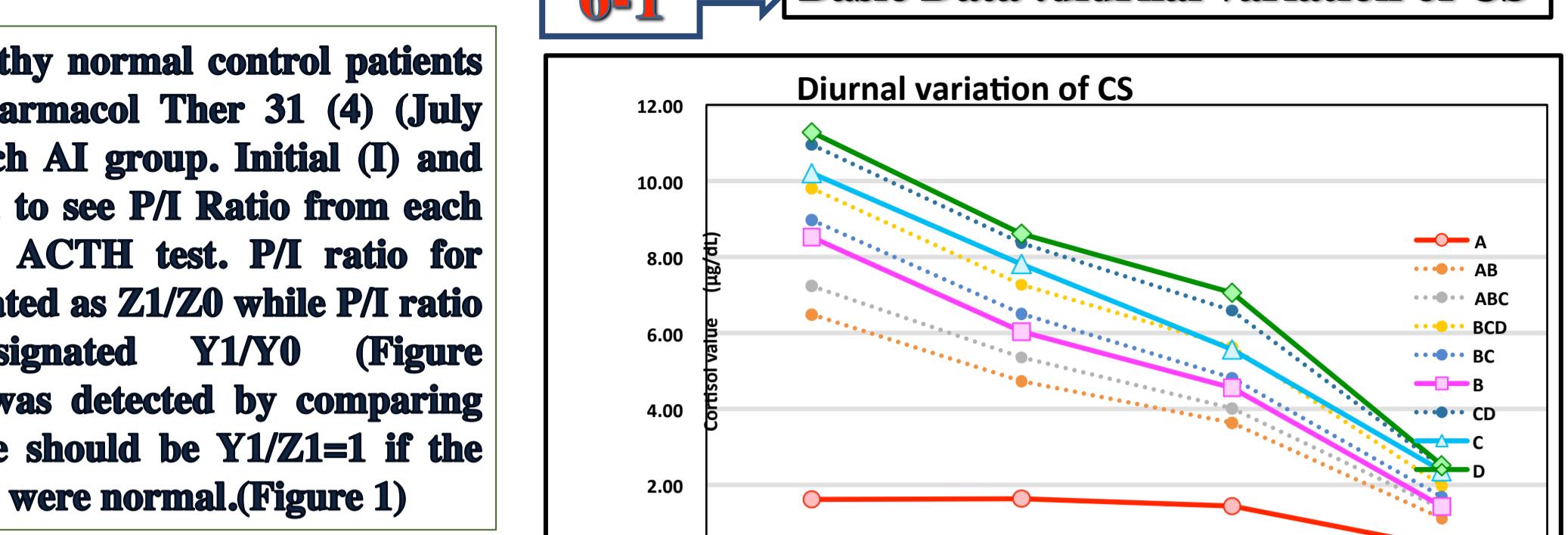
4 → Standard curve for rapid ACTH test to obtain AR :

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)



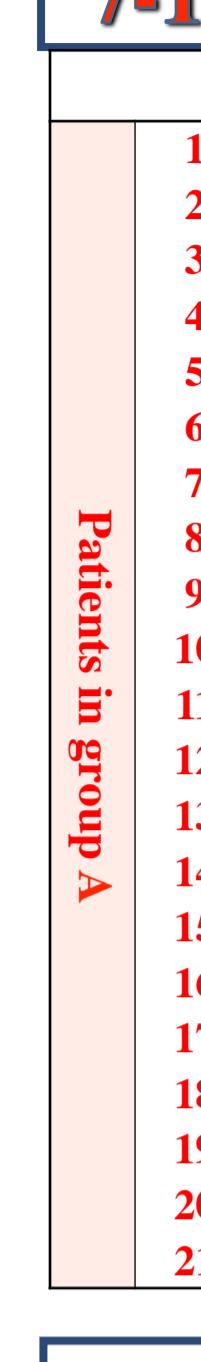
6-1

Basic Data :diurnal variation of CS



7-1

Result-1



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

Background of those with severe AI:
(1) Symptoms of AI after gradual withdrawal of systemic CS
Use of Biologics: 9 / 21=42.9%
*mepolizmab
+omalizmab

(2) Symptoms after viral infection
(3) Symptoms after lymphoma therapy
(4) Symptoms after orthopedic therapy
(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
No9:HT; No19:MI
No1:OK, No2:OY;No16:SK, No21:NN

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.

7-2

Result-2

