IDWeek 2013

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Risk factors that can predict adrenal insufficiency in fever of unknown origin

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Background

Although adrenal insufficiency is one of the causes of fever of unknown origin (FUO), it is often mistaken for infectious disease in clinical settings. To date, sufficient analysis has not been conducted on the frequency and characteristics of adrenal insufficiency among fever of unknown origin, and the target patient to recommend tests to differentiate adrenal insufficiency among FUO patients is not clear. The purpose of this study is to analyze factors that can predict adrenal insufficiency in patients with FUO, and to set a target to recommend tests for diagnosis of adrenal insufficiency.

Methods

- **Study setting**
  - The medical records of all adult patients (age ≥ 19 years) with FUO between 1 July, 2019 and 30 June, 2020 were retrospectively reviewed.
  - Study hospital: An 846-bed a tertiary-care hospital in South Korea
- **Inclusion**
  - Inpatient with ≥ 19 years old.
  - Patients who were referred to ID department for consultation of FUO
    - ✓ FUO cases were confirmed by an ID specialist.
  - Fever event (≥37.8℃) was present within 48 hours before and/or after the ACTH stimulation test.
- **Definition of the adrenal insufficiency**
  - Post-stimulation cortisol < 20μg/dL (30min and 60min)
- **End points**
  - The proportion of patients diagnosed with adrenal insufficiency among patients with FUO
  - Clinical characteristics of patients diagnosed with adrenal insufficiency among patients with FUO
- **Statistical analysis**
  - Categorical variables were analyzed by the chi-square test.
  - Continuous variable were analyzed by the independent t-test or Mann-Whitney U test.
  - Logistic regression analysis was conducted to find factors that could predict adrenal insufficiency in patients with FUO.

Results

Table 1. Comparison of clinical characteristics of FUO patients with adrenal insufficiency to others

	Adrenal insufficiency (n = 61)	Others (n = 141)	P-value	Total (n = 202)
Underlying co-morbidities				
Charlson's comorbidity index score	2.36±1.88	1.85±2.06	0.016	2.00±2.01
Connective tissue disease (%)	18 (29.5)	9 (6.4)	<0.001	27 (13.4)
Chronic kidney disease (%)	8 (13.1)	4 (2.8)	0.005	12 (5.9)
Other medical conditions				
Use of immunosuppressants within 3 months (%)	19 (31.1)	9 (6.4)	<0.001	28 (13.9)
Use of corticosteroid within 3 months (%)	12 (19.7)	5 (3.5)	<0.001	17 (8.4)

- Patients with adrenal insufficiency accounted for 30.1% of the total FUO patients.
- The adrenal insufficiency group showed a higher Charlson's comorbidity index score than the control group, and the proportion of patients with connective tissue disease and chronic kidney disorder was higher, as well.
- Compared to the control group, the adrenal insufficiency group used more immunosuppressants or corticosteroid within 3 months.

Table 2. Comparison of clinical manifestations of FUO patients with adrenal insufficiency to others

	Adrenal insufficiency (n = 61)	Others (n = 141)	P-value	Total (n = 202)
Hypotension (%)	13 (21.3)	15 (10.6)	0.044	28 (13.9)

- The adrenal insufficiency group had a higher rate of hypotension than the control group.

Table 3. Comparison of initial laboratory findings characteristics of FUO patients with adrenal insufficiency to others

	Adrenal insufficiency (n = 61)	Others (n = 141)	P-value	Total (n = 202)
TSH (μIU/mL)	2.68±3.24	1.88±1.71	0.761	2.08±2.19
Free T4 (ng/dL)	1.12±0.32	1.17±0.27	0.138	1.16±0.28
Glucose (mg/dL)	128.66±36.66	147.82±65.70	0.141	141.98±58.95
CRP (mg/dL)	11.96±10.57	13.81±10.95	0.183	13.26±10.84
Procalcitonin (ng/mL)	9.70±25.38	4.66±12.39	0.554	6.04±16.97
Sodium (mEq/L)	137.62±4.80	136.25±5.01	0.053	136.67±4.97
Potassium (mEq/L)	3.79±0.55	3.80±0.49	0.884	3.80±0.50
WBC count (cells/mm³)	9.27±6.30	10.54±5.82	0.025	10.15±5.98
Eosinophil count (%)	4.38±9.96	1.70±2.10	0.070	2.52±5.87
Hemoglobin (g/dL)	9.95±1.76	10.44±1.79	0.023	10.29±1.79
BUN (mg/dL)	22.01±13.14	21.57±16.17	0.361	21.71±15.28
Creatinine (mg/dL)	1.39±1.61	1.05±1.57	0.044	1.15±1.59
Albumin (g/dL)	2.84±0.51	3.04±0.42	0.009	2.98±0.46
Calcium (mg/dL)	8.25±0.94	8.49±0.60	0.070	8.42±0.73

- Compared to the control group, the adrenal insufficiency group had lower WBC count, hemoglobin, and albumin levels, and higher creatinine levels.

Table 4. Comparison of clinical outcomes of FUO patients with adrenal insufficiency to others

	Adrenal insufficiency (n = 61)	Others (n = 141)	P-value	Total (n = 202)
Corticosteroid supplement (%)	35 (57.4)			
Duration of corticosteroid supplementation, mean±SD	21.49±42.43			
Clinical Outcomes				
Day of defeverence after diagnosis, mean ± SD	3.53±2.97			
Recurrence of adrenal insufficiency combined with fever within 12 months (%)	3 (4.9)			
Hospitalization duration , mean ± SD	30.33±25.77	29.55±27.23	0.955	29.79±26.73

Table 5. Risk factors for adrenal insufficiency of FUO patients

Variables		Univariate analysis		Multivariate analysis	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Age ≥ 65					
No	84	1			
Yes	118	1.26 (0.68-2.33)	0.462		
Female sex					
No	95	1			
Yes	107	0.97 (0.53-1.77)	0.924		
Charlson's comorbidity index ≥ 2					
No	103	1			
Yes	99	1.62 (0.88-2.97)	0.119		
Use of immunosuppressant within 3 months					
No	174	1		1	
Yes	28	6.64 (2.79-15.77)	0.000	6.06 (1.82-20.13)	0.003
Use of corticosteroid within 3 months					
No	185	1		1	
Yes	17	6.66 (2.23-19.88)	0.001	8.23 (1.35-50.17)	0.022
Hypotension					
No	174	1			
Yes	28	2.28 (1.01-5.13)	0.048		
Sodium ≥ 136.7					
No	93	1		1	
Yes	108	2.02 (1.08-3.76)	0.027	3.43 (1.49-7.88)	0.004
WBC count ≥ 10150					
No	110	1			
Yes	92	0.52 (0.28-0.97)	0.038		
Eosinophil ≥ 2.5					
No	145	1			
Yes	55	1.81 (0.94-3.48)	0.074		
Hemoglobin ≥ 10.3					
No	105	1		1	
Yes	97	0.45 (0.24-0.84)	0.012	0.45 (0.20-1.04)	0.062
Albumin ≥ 3					
No	79	1			
Yes	101	0.54 (0.28-1.02)	0.057		
Calcium ≥ 8.4					
No	77	1		1	
Yes	88	0.39 (0.20-0.77)	0.006	0.31 (0.14-0.71)	0.005

- Logistic regression analysis : the following factors are found to be able to predict adrenal insufficiency
  - ✓ Immunosupressants use within 3 months (OR 6.06)
  - ✓ Systemic steroid use within 3 months (OR 8.23)
  - ✓ Sodium ≥ 136.7mEq/L (OR 3.43)
  - ✓ Calcium ≥ 8.4mg/dL (OR 0.39)

- Among the patients with adrenal insufficiency, 57.4% of the patients received systemic steroid.
- The mean period until defeverence after the diagnosis of adrenal insufficiency was 3.53±2.97 days.
- There was no difference in hospitalization period between patients with adrenal insufficiency and other patients.

Conclusions: In patients with immunosuppressants or systemic steroid prescription within 3 months, or with high sodium levels or low calcium levels, ACTH simulation test should be performed to discriminate adrenal insufficiency.