ORIGINAL RESEARCH

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Epidemiology of Adrenal Insufficiency Among Elderly Patients in a Convalescent Care Unit and One Year Outcome

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Abstract

Objective: Adrenal insufficiency (AI) is associated with significant morbidity and mortality. The diagnosis of AI in elderly people is difficult with its non-specific presentation. The aim of this study is to describe the epidemiology, pattern of comorbidity and one-year outcome among elderly people after their initial diagnosis of AI.

Materials and Methods: Patients aged >65 years, who underwent the Short Synacthen test (SST) done during the period of 1.1.2014 to 30.6.2019, were retrieved. Basic demographic information, comorbidities as measured by the Charlson Comorbidity index (CCI), cause for admission, length of stay, one year unplanned readmission and death were recorded.

Results: Two hundred forty two patients with the mean age of 79.6 (standard deviation 8.75) were identified. The causes for admission were pneumonia (22.3%), electrolytes abnormalities (11.6%) urinary tract infection (UTI) (8.6%) and poor oral feeding (7.8%). Ninety four (38.3%) were diagnosed to have AI. The most common indication for SST was electrolytes abnormalities. Unplanned readmission was present in 52.7% of patients. Inpatient mortality was 11.6% and one year mortality was 44.8%. There was no statistically significant difference between the AI and normal response group in age, gender, CCI score, length of stay, cause for admission, indication for SST and mortality. However, the AI group had a much lower baseline cortisol level (389 nmol/L vs. 192.4 nmol/L, p<0.001).

Conclusion: This unrecognized group of elderly AI patients presents non-specifically. Respiratory and UTIs were the most common cause of admission. Physicians should be more alert on this easily unrecognized problem in the elderly. What is known on the subject and what does the study add: The incidence of AI in elderly subjects is on the rising trend, yet, it is easily unrecognized; this study highlights the importance of infection that contributes to AI development and the non-specific presentation of this disease in older population.

Keywords: Adrenal insufficiency, elderly, epidemiology

Introduction

Adrenal insufficiency (AI) is an uncommon problem, but it can be associated with significant morbidity and mortality (1). Causes of AI can be primary or secondary. Primary AI is due to inadequate production of adrenocorticosteroids as a result of damage to the adrenal gland. Common etiologies include autoimmune disease, infection, tumour or hemorrhage. Secondary AI is far more common than primary AI (2,3). It is due to disease in the pituitary or hypothalamus, causing inadequate adrenocorticotropic hormone production, which in turn reduces stimulation to adrenal cortex on corticosteroid production. Surveys in the Western population revealed that the prevalence of primary and secondary AI increased with time. The reported prevalence rate of primary and secondary AI in the 1990s was 9-14/10^5 and 15-28/10^5 population respectively (2,4) which was much higher than those reported in the 1960s. However, a Japanese study has observed that the incidences of primary

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AI decreased with time (5). On the contrary, a nationwide Taiwanese study showed that the annual incidence of AI had continuously increased and elderly patients were accounted for the majority of this increase (6).

The diagnosis of AI is non-specific. It usually presented with variable symptoms such as fatigue, fever, poor appetite or gastrointestinal discomfort. It can progress to adrenal crisis with electrolytes disturbances, change of conscious level, shock and even death. Making the diagnosis of AI in older people is even more difficult. Older people have multiple comorbidities, and the symptoms might be mistaken as ageing processes (7). Epidemiological studies about AI among the elderly population are limited. Contributing factors and the signs and symptoms of AI are not well studied. Prevention of an adrenal crisis requires early recognition and prompt initiation of treatment. However, not much data are available on the incidence and prevalence of AI, and the low awareness among medical professionals may lead to adverse outcome in an unrecognized adrenal crisis.

This study aims to describe the demographic profile, the pattern of comorbidity, contributing factors for older adults with AI and the 1-year outcome after the diagnosis of AI.

Materials and Methods

Hospital records were retrieved from 3 extended care units of a hospital network in Hong Kong. Case notes of subjects with age >65 and with Short Synacthen test (SST) done during the period 1.1.2014 to 30.6.2019 were retrieved. Those who were admitted as day-procedure for SST were excluded. Patient's age, gender, place of residence, comorbidities measured by Charlson Comorbidity index (CCI) (8) on admission, principal diagnosis and length of stay were recorded. An infection was classified as principal diagnosis or secondary diagnosis based on the condition that the disease was caused by an organism such as urinary tract infection (UTI), pneumonia or lower respiratory tract infection (LRTI) or where an infectious agent was coded (9). A virus was identified as present when specific viral agent was identified or where a diagnostic code had a viral agent included (9). Gastroenteritis was recorded by any code that specifies gastroenteritis whether it can be viral, bacterial or non-infectious in origin. Pneumonia/LRTI/chest infection was classified as pneumonia. Acute bronchitis and chronic obstructive pulmonary disease (COPD) with mentioning of infection were also considered as chest infection. In contrast, COPD, asthmatic exacerbation or bronchiectasis where the infection was not mentioned were not considered as infection.

Baseline cortisol level were recorded. AI is diagnosed by SST. For standard dose SST using 250 mcg tetracosactin, a failure of the cortisol level taken at 30 min to rise >550 nmol/L from baseline is considered as positive (10). For low dose SST using one mcg of tetracosactin, a failure of 30 min cortisol to rise >400 nmol/L from baseline is considered as positive (11). Indication for SST were be recorded. These include hypotension, electrolytes abnormality, unexplained poor general status, poor appetite, weight loss and other indications were collected. All subjects will be further followed for one year after their diagnosis. The proportion of patients with unplanned hospital readmission will be calculated. The discharge diagnosis and death were analyzed.

Subjects who failed the SST were considered as cases while those showed a normal response were considered as the control group.

Statistics

Descriptive statistics on baseline demographic variables as mean +/- standard deviation (SD) or median where appropriate. Between-groups comparison on demographic variables, possible precipitating causes, length of stay and inpatient mortality will be analyzed by t-test or Mann-Whitney U test for continuous data and x^2 test for categorical data. Hospital readmission rate and mortality at one year were also compared. A p-value of <0.05 is considered as statistically significant.

This study is approved by the Hong Kong Hospital Authority Cluster Hospital Research Ethics Committee.

Results

There were a total of 292 SST done during the period of 1.1.2014 to 30.6.2019. Among them, 242 subjects met the inclusion criteria, and their records were retrieved. Figure 1 shows the consort flow diagram. The mean age was 79.6 (SD 8.75). There were 135 male subjects (55.6%). One hundred seventy one low dose SST and 72 standard dose SST were performed. The most common cause for hospitalization was pneumonia (54, 22.3%) followed by electrolytes abnormalities (28, 11.6%), UTI (21, 8.6%) and poor oral feeding (19, 7.8%). There were 28 subjects died during the index admission. The in-patient mortality rate on the index admission was 11.6%. During the one-year observation period after discharge from the index hospital admission, 152 subjects were readmitted with a median number of readmission of 2,96 of them were dead in one year and the one year mortality rate was 44.8%. Indications for SST was shown in Figure 2. One hundred fourty eight (61.15%) of them have a normal response to SST while 94 were diagnosed as AI (38.84%). There was no statistically significant difference between the two groups on age, CCI, causes for hospitalization and indications for SST. For electrolytes abnormalities, all of them were due to hyponatremia. There was also no statistical significant difference in hospital length of stay, inpatient and one year mortality between those who have normal and failed response to SST. However, the adrenal insufficient group has a much lower baseline cortisol level than the normal response

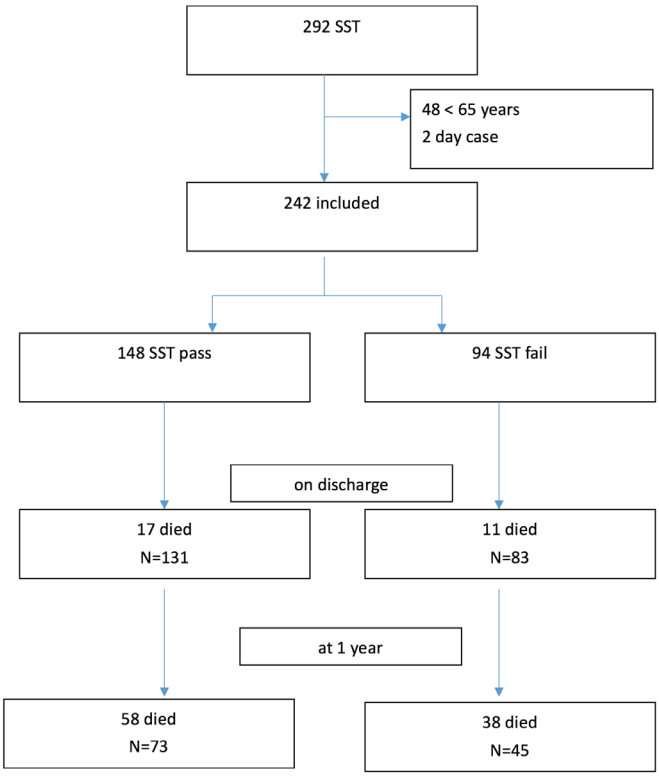

Figure 1. Consort flow diagram

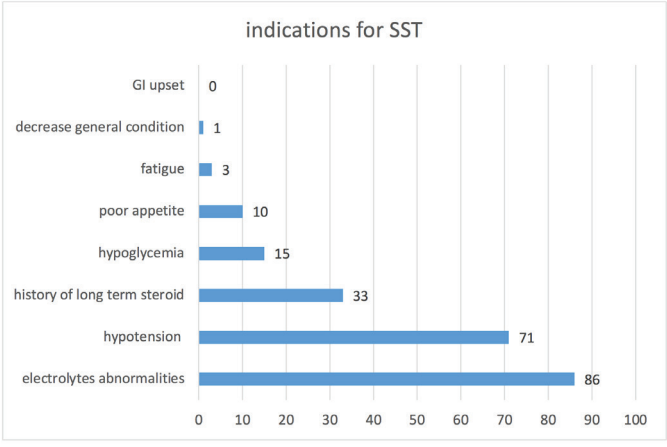

Figure 2. Indications for SST among the whole sample group each bar represents number of case

SST: Short Synacthen test, GI: Gastrointestinal

group (Table 1).

Discussion

There were many causes for AI. Many studies have reported on primary and secondary causes of AI, mostly related to brain tumour. Primary AI is rare with an estimated incidence of 0.56-0.62/10^5 (4), while for secondary AI, no definite data on the incidence rate is available (12). A study in Taiwan (6) reported an increasing incidence of all-cause AI over a 13-year period of 6.4 to 15.2/10^5. This can be attributed by an ageing population, increasing incidence of underlying diseases that lead to AI and perhaps, better diagnostic ability. The peak age for primary AI is reported to be around 40s while for secondary AI, it was at the 6th decade of life (2). In our study, the mean age for all causes of AI is around 80, which is much older than those reported previously (2). In spite of this, it seems that AI in Asian/Chinese ethnicity is more common among the older age group. The proportion of subjects with AI with age >80 is on the rising trend as reported in a nationwide survey (6). The incidence rate was 10.6% in 1997, rising to more than twofold to 27% in 2008. In echo with this, it is suggested that the growing number of AI in the elderly population may be due to an increase in the incidence of disease that precipitates adrenal failure. Moreover, older people have a lower sensitivity of the hypothalamus-pituitary-adrenal axis (HPA) to cortisol feedback (13) which might explain the higher incidence of AI among them. For secondary AI, sudden discontinuation of exogenous glucocorticoid therapy or hypothalamic-pituitary-adrenal axis suppression due to long term steroid use and inadequate cortisol production in response to physiological stress is common among elderly patients with long term steroid use due to COPD or arthritic conditions (14).

This study reveals the non-specific presentation of AI. Most cases of AI were diagnosed in an acute hospital setting in which the classical signs and symptoms of AI such as hypotension, hypoglycemia, hyponatremia will be presented to an acute hospital for urgent medical treatment. Those cases that managed in extended care and rehabilitation units were usually more stable with limited symptoms that seldom arouse awareness on the possibility of adrenal problem. In spite of this, we were still able to detect a certain proportion of patients who were undiagnosed. We postulated that this underdiagnoses of AI might be due to lack of unawareness or the non-specific presentation of AI in older adults.

Our findings showed that pneumonia was the most common cause for acute hospital admission in subjects with newly diagnosed AI. Bacterial infection will impact subjects with AI. Studies have shown that patients with hypoadrenalism have a higher risk of bacterial infection (15,16). Furthermore, the presence of a bacterial infection will provoke a strong inflammatory cytokine response that stimulates the HPA to increase cortisol production. This can lead to a reduction in inflammation and protect against tissue damage. However, in the case of hypoadrenalism, the lack of an increase in cortisol production will lead to a severe inflammatory response which may result in tissue damage and systemic effects including hypotension, shock and organ failure (17). A study in Japan (18) showed that infectious disease was the major cause for inducing adrenal crisis. Another study (19) supported the finding of a close relationship between the severity of community-acquired pneumonia, inpatient mortality and the average

Table 1. Characteristics of patients undergoing Short Synacthen test

	SST pass (N=148)	SST fail (N=94)	p
Age (years)	79.43 (SD 9.17)	79.61 (SD 8.75)	0.706
CCI (median)	2	2	0.742
Gender (male)	82 (57.77%)	52 (55.32%)	1
Old age home residents	36 (24.32%)	25 (26.6%)	0.762
Length of hospitalization (days)	38.68 (SD 64.77)	31.39 (SD 46.45)	0.345
Unplanned readmission	91 (64.48%)	61 (65.59%)	0.584
In patient mortality	17 (11.4%)	11 (11.7%)	1
One year mortality	58 (44.2%)	38 (45.7%)	0.892
Baseline cortisol level (nmol/L)	389.89 (SD 143.56)	192.41 (SD 130.67)	<0.001 (95% CI -233.15, 161.81)
Indications for SST			
Hypotension	49 (33.1%)	21 (22.3%)	0.082
Electrolytes abnormalities	56 (37.83%)	30 (31.9%)	0.409
Fatigue	1 (0.6%)	2 (2.1%)	0.335
Poor appetite	6 (4.1%)	9 (9.6%)	0.591
Hypoglycemia	7 (4.7%)	8 (8.5%)	0.278
History of long term steroid	15 (10.1%)	18 (19.1%)	0.055
Decrease general condition	8 (5.4%)	8 (8.5%)	0.428

SST: Short Synacthen test, CCI: Charlson Comorbidity index, SD: Standard deviation

length of hospitalization with adrenal function. A recent study reported that infection was the most prevalent comorbidity for adrenal crisis among adrenal insufficient subjects, followed by respiratory disease (20). There are many risk factors for adrenal crisis among subjects with chronic AI. It is well reported that initial illness, especially sepsis, was associated with AI (21). From our study, there were a number of patients who were newly diagnosed as having AI only after they were transferred to convalescence unit. This reiterated the fact that presentation of AI is very vague and easily missed. This group of patients may have more comorbidities and may be much older in age. The altered HPA function in older people would have an influence on the onset of adrenal crisis (22). Therefore, adrenal failure thus developed would lead to a more severe condition than the younger population and higher incidence as well. A population survey found that excluding those with chronic AI, patients with the adrenal crisis were older and had more comorbidities than those with primary and central AI (23). Thus, physicians caring for patients with AI, besides attention on the general status and predisposing conditions, the patient's age and comorbidities should also be taken into account.

The most common indication for performing SST in our sample population was electrolytes abnormalities. This is one of the alerting sign for the diagnosis of AI (24). AI is not a common cause for hyponatremia (25). However, it has been described that a low serum sodium level is present in 80% of cases with adrenal crisis (26). In contrast, a more recent study (6) showed that among 4.85% of patients with newly diagnosed AI has electrolytes imbalance. The author postulated that the severity of AI in their population group does not reach the level of adrenal crisis. This is in accordance with the setting of non-acute convalescence unit diagnosing AI. Those patients with a borderline adrenal reserve will have subtle signs and symptoms that would have been detected in convalescence in which the longer length of hospital stay would enable clinicians to have a thorough investigation of non-specific presentations. Thus a high index of suspicion should help to alert clinicians on the diagnosis of AI.

The second most common indication for performing SST is unexplained hypotension. Those with very low blood pressure or even shock would have been detected during an adrenal crisis. Those frail elderly patients with relatively low blood pressure, but asymptomatic, would have been missed. Clinicians managing patients with asymptomatic hypotension may consider this low blood pressure was due to dehydration, occult sepsis or side effects of drugs. These diagnostic uncertainties may differ between clinicians with varying level of experience. Both hypotension and electrolytes imbalance was only present in 22-31% of our subjects. This low prevalence of the classical signs and symptoms of AI warrant thorough evaluation of elderly patients with non-specific signs and symptoms. Patients with chronic AI may present non-specifically and only when exposed to medical conditions such as infection will result in adrenal crisis and mortality.

Inpatient and one year mortality were high in our study population. 11.6% of our sample died during the index hospitalization while the one year mortality was up to 40%. This reflects the severity of medical problems and the poor health status of our study sample. However, our study showed

that the one year mortality rate were similar between subjects with or without AI. This could represent the effectiveness of the replacement therapy. As such, offering more screening in suspected patients may benefit more patients with undiagnosed AI.

Furthermore, it is postulated that those underdiagnosed hypoadrenal patients would have their medical illness treated in acute hospital and discharge back home directly. There is a possibility that they will develop adrenal crisis after another episode of medical illness. They are a group of vulnerable patients with potentially lethal outcome. It is suggested that those frail elderly with a low or borderline electrolytes abnormalities and/or unexplained low blood pressure should have screening for AI.

Management of AI is practically difficult in older patients. The pharmacokinetics and pharmacodynamics of drugs change with age. Polypharmacy, which is common in the elderly population, complicate drug-drug interaction. Cognitively impaired elderly patients will have compliance issues (27), and the increasing prevalence of comorbid conditions with ageing will further influence the disease management. Typical signs and symptoms of infection such as fever may not be experienced by elderly patients. Thus, the stress dose of glucocorticoid may not be administered. Furthermore, delirium is common among elderly with sepsis, self-management of taking extra steroid dose will not be possible.

There were several limitations in our study. Only database on SST was retrieved. We cannot identify the true incidence of AI among subjects in the convalescence care unit. We could not differentiate primary from secondary AI, although the management for both causes of AI remains the same. The severity of AI cannot be adequately assessed. We only have data on the baseline cortisol and electrolytes level. There was no information on the clinical state of the subjects nor the blood pressure response. Details on drug prescription were not recorded. The cause for hospital readmission were not known. The incidence of AI may be under-estimated since those cases that were diagnosed and treated in ambulatory setting were not included. There was no information on the infectious agent causing the sepsis.

Finally, we cannot ascertain the cause and effect on the relationship between AI and as it was only a retrospective study.

Conclusion

A certain proportion of elderly people with AI were unrecognized in acute hospital and present non-specifically. Infection of the chest and urinary tract were the most common comorbidity. Hypotension was the most common manifestation of AI among convalescence care elderly patients. Clinicians should be more aware of the signs and symptoms of AI, which is easily overlooked in the elderly population.

Ethics

Ethics Committee Approval: This study is approved by the Hong Kong Hospital Authority Cluster Hospital Research Ethics Committee (date: 18.12.2019, number: KC/KE- 19-0218/ER-2).

Informed Consent: Since this is a retrospective study, no patient consent is required.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: D.K.Y.M., Design: D.K.Y.M., Data Collection or Processing: D.K.Y.M., S.P.M., S.K.F.T., Analysis or Interpretation: D.K.Y.M., Literature Search: D.K.Y.M., Writing: D.K.Y.M., S.P.M., S.K.F.T.

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References

1. Bergthorsdottir R, Leonsson-Zuchrisson M, Oden A, Johannsson G. Premature mortality in patients with Addision's disease: a population-based study. J Clin Endocrinol Metab 2006;91:4849-4853.
2. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881-1893.
3. Fernandez-Rodriguez E, Lopez-Raton M, Andujar P, Martinez-Silva IM, Cadarso-Suaraez C, Casanueva FF, Bernabeu I. Epidemiology, mortality rate in a homogenous population of hypopituitary patients. Clin Endocrinol 2013;78:278-284.
4. Lovas K, Husebye ES. High prevalence and increasing incidence of Addison's disease in Western Norway. Clin Endocrinol (Oxf) 2005;56:787-791.
5. Nomura K, Demura H, Sacuta T. Addison's disease in Japan: characteristics and changes revealed in a nationwide survey. Intern Med 1994;33:602-606.
6. Chen YC, Lin YH, Chen SH, Chen YC, Chou LF, Chen TJ, Hwang SJ. Epidemiology of adrenal insufficiency: A nationwide study of hospitalizations in Taiwan from 1996-2008. J Chin Med Assoc 2013;76:140-145.
7. Tayal SC, Bansal SK, Chadha DK. Hypopituitarism: a difficult diagnosis in elderly people but worth a research. Age Ageing 1994;23:320-322.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
9. Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infection. BMC endocr disorder 2014;14:79.
10. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003;139:194-204.
11. Park YJ, Park KS, Kim JH, Shin CS, Kim SY, Lee HK. Reproducibility of the cortisol response to stimulation with the low dose (1microg) of ACTH. Clin Endocrinol (Oxf) 1999;51:153-158.
12. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881-1893.
13. Beale E, Zhu J, Belzberg H. Changes in serum cortisol with age in critically ill patients. Gerontology 2002;48:84-92.
14. Scheutz P, Christ-Crain M, Schild U, Suess E, Facompre M, Baty F, Nusbaumer C, Brutsche M, Müller B. Effects of a 14-day course of systemic corticosteroids on the hypothalamic-pituitary-adrenal axis in patients with

acute exacerbation of chronic obstructive pulmonary disease. BMC Pul Med 2008;8:1.

15. Smans LC, Souverein PC, Leufkens H, Hoepelman AI, Zelissen PM. Increased use of anti-microbial agents and hospital admission for infections in patients with primary adrenal insufficiency: a cohort study. Eur J Endocrinol 2013;168:609-614.
16. Chen YC, Chen YC, Chou LF, Chen TJ, Hwang SJ. Adrenal insufficiency in the elderly: a nationwide study of hospitalization in Taiwan. Tohoku J Exp Med 2010:221:281-285.
17. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analysis. J Epidemiol Community Health 2012;66:1177-1181.
18. Takayanagi R, Miura K, Nakagawa H, Nawata H. Epidemiologic study of adrenal gland disorders in Japan. Biomed Pharmacother 2000;54(Suppl 1):164s-168s.
19. Gotoh S, Nishimura N, Takanashi O, Shiratsuka H, Horinouchi H, Ono H, Uchiyama N, Chohnabayashi N. Adrenal function in patients with community-acquired pneumonia. Eur Respir J 2008;31:1268-1273.
20. Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Clinical features and practice patterns of treatment for adrenal crisis: a nationwide cross-sectional study in Japan. Eur J Endocrinol 2017;176:329-337.
21. Ben-Shlomo A, Mirocha J, Gwin SM, Khine AK, Liu NA, Sheinin RC, Melmed S. Clinical factors associated with biochemical adrenal-corticoid insufficiency in hospitalized patients. Am J Med 2014;127:754-762.
22. Gaffey AE, Bergeman CS, Clark LA, Wirth MM. Ageing and the HPA axis: stress and resilience in older adults. Neurosci Biobehav Rev 2016;68:928-945.
23. Iwasaku M, Shinzawa M, Tanaka S, Kimachi K, Kawakami K. Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: a retrospective cohort study. BMC Endocr Disord 2017;17:58.
24. Jacobi J, Schnellhardt S, Kulschewski A, Amann KU, Kuefner MA, Eckardt KU, Hilgers KF. An unusual cause of hyponatremia. Nephol Dial Transplant 2010;25:998-1001.
25. Winchester Behr T, Somnenblick M, Nesher G, Munter G. Hyponatremia in older people as a sign of adrenal insufficiency: a case control study. Intern Med J 2012;42:306-310.
26. Arlt W. The approach to those adult with newly diagnosed adrenal insufficiency. J Clin Endocrinol Metab 2009;94:1059-1067.
27. Wynne HA, Blagburn J. Drug treatment in ageing population: practical implication. Maurtias 2010;66:246-250.