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Detail Investigation of Frequent Nocturia and its Improvement by the Administration of Diuretic

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Abstract

Background: For elderly people, nocturia has been often found associated with other diseases. **Case presentation:** The case is 88-year-old male with hypertension, Cardiovascular Disease (CVD), Diabetes, Chronic Kidney Disease (CKD). He developed nocturia and insomnia, and then checked daily water balance by himself. **Results:** Basic situation showed water intake/urine volume were 750mL/1030mL/day, in which urine ratio of day/night was 27%/73% with waking up twice during night. He was given furosemide 20mg, per os at 1500h. Same study showed 960mL/1090 mL, and urine ratio as 77%/23% with no waking up. **Discussion and Conclusion:** From some reports, Odds Ratio (OR) for combination of nocturia shows 1.25 for hypertension, 1.23/1.74 for CVD (mild/severe). Consequently, current treatment would contribute adequate managements for nocturia problem.

Keywords: Nocturia, Cardiovascular disease, Chronic kidney disease, Furosemide, Insomnia, Hinohara-ism.

Abbreviations: CVD-Cardiovascular Disease, CKD-Chronic Kidney Disease, LUTS-Lower Urinary Tract Symptoms, MCI-Mild Cognitive Impairment, ASCVDs-Atherosclerotic Cardiovascular Diseases, CHD-Coronary Heart Disease, eGFR-estimated Glomerular Filtration Rate, LAE-Left Atrial Enlargement, NHANES-National Health and Nutrition Examination Survey.

Introduction

For elderly people, nocturia and insomnia have been often found. Such situations are rather common from health and medical points of view. As to nocturia, systematic review was conducted for neurological diseases using 21-year data. Out of 6262 reports, 43 adequate papers were screened for analyzed data [1]. The results showed that complicated causes were found and applicable guidance would be practical for decreasing various risks. Another systematic review was tried for nocturia and insomnia. The data was checked for 1658 titles and summaries. Among them, 23 applicable papers were selected for detail analysis [2]. As a result, insomnia is often influential for nocturia, however it seems to be overlooked. Furthermore, it has been involved in bladder filling, easy waking up, sleep apnea and other factors. Related to these, Lower Urinary Tract Symptoms (LUTS) would remarkably decrease health states, QOL and ADL for elderly men and female [3,4]. Frequent nocturnal urination (Nocturia) has been one of the common bothersome symptoms for elder people [5,6]. Furthermore, insomnia (sleep disturbance) associated with nocturia may bring decreased QOL and ADL.

This problem may be from several unfavorable outcomes including Cardiovascular Disease (CVD), hypertension, diabetes, depression,

dementia, Mild Cognitive Impairment (MCI), accidents, falls and other cases [7,8]. Thus, it is not easy to clarify the detail combination and relationship of nocturia, insomnia and other complex cases [9]. Insomnia may show a large influence on Health-Related Quality Of Life (hsQOL) than nocturia [10]. Furthermore, a longitudinal study showed the influence of insomnia on nocturnal urine problems [11]. Authors and co-researchers have continued medical practice and clinical research for long, such as anti-aging medicine, diabetes, hypertension, Atherosclerotic Cardiovascular Diseases (ASCVDs), Metabolic Syndrome (MET-S), and others [12-14]. Furthermore, primary care medicine, Complementary and Alternative Medicine (CAM) and Integrative Medicine (IM) were included in our working area [15,16]. We have experienced lots of patients with various health and medical problems. Recently, an impressive case with nocturia was observed who has conducted his detail investigation of water balance by himself. The data and some perspective and discussion will be described in this case report.

Case Report

History of Present Illness: The patient is 88-year-old male with Type 2 Diabetes (T2D), hypertension, Coronary Heart Disease (CHD) and hyperuricemia. His general condition has been stable for more than 7

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years. He had checked his daily profile of blood pressure in June 2020 and changed the time of Antihypertensive Agent (AHA) [13]. After that, he has received the heart operation of aortic stenosis in Tokushima Red Cross Hospital in Feb 2021. It was successfully performed at the age of 86 years old. His condition was stable after that. He felt some problem of frequent nocturia from Dec 2021. He visited the specialist of urologist for consulting the treatment of nocturnal inconvenience.

Social history: He had been a chemical engineer during his life. He had been working in Toho Rayon Company in Tokushima and Shikoku Kasei Chemical corporation in Shikoku Island. He has made a lot of achievements in the chemical field such as obtaining more than 20 patents in his research. Furthermore, he has been one of the members of New Elderly Association (NEA), which had been established by an eminent physician, Shigeaki Hinohara, who worked until 105 years in International St. Luke hospital, Tokyo. The case has fully understood the way of life of Hinohara-ism, and actually practiced in recent years. He has understood and practiced Hinohara-ism every day, such as enjoying ground golf, karaoke, ballroom dancing, leading to his stable mind and body. He has continued to have such adequate background from psychological and social points of view.

Physical examination: He has showed unremarkable findings in the physical examination, and unremarkable specific symptoms or signs related to T2D, CHD and hypertension. He did not have particular diabetic complications, such as neuropathy, retinopathy or nephropathy. His Body Mass Index (BMI) was 20.1 kg/m². He showed slightly decreased Estimated Glomerular Filtration Rate (eGFR), but no apparent symptoms concerning Chronic Kidney Disease (CKD).

Laboratory exams: Main results of laboratory exams in February 2022 were as follows: WBC 7200/ μ L, RBC 3.31 x 10⁹/ μ L, Hb 10.3 g/dL, Plt 11.4 x 10⁴/ μ L, HbA1c 6.0%, blood glucose 136 mg/dL, AST 26 U/mL, ALT 14 U/mL, LDH 189 U/L (124-222), HDL-C 69 mg/dL, LDL-C 82 mg/dL, TG 154 mg/dL, Alb 3.9 g/dL, BUN 31 mg/dL, Cre 1.24 mg/dL, eGFR 42 mL/min/1.73m², Na 140 mmol/L, K 4.8 mmol/L, BNP 61.7 pg/mL (-18.4). Urinalysis showed Na 54 mEq/L, Cre 215 mg/dL, estimated NaCl excretion 4.3 g/day. Echocardiogram of the heart showed the stable results. They are i) Dimension: IVSd 11mm, LVPWd 10mm, LVDd 41mm, LVDs 25mm, EF (Teich) 59%, FS 38% LAD 33mm, IVC 14mm, respiratory fluctuation (+), diastolic dysfunction E 74 cm/s, A 89 cm/s, ii) A valve: AR (-), Ascending aorta 31mm, AVF 2.1m/s, AVA 1.00 cm², P-PG 18 mmHg, LVOF 0.7 m/s, m-PG 9 mmHg, LVOF (VTI) 16.7 cm, LVOT 19mm, iii) Wall motion: asynergy was not found. From these analysis, normal prosthetic valve function was diagnosed.

Medication: He has been provided several kinds of medical agents for T2D, CHD, hypertension, hyperuricemia, post-operative state of aortic stenosis in Feb 2021 and insomnia. His recent prescription can be summarized as follows: 1) sitagliptin phosphate hydrate 50mg, 2) nifedipine 20mg, telmisartan 40mg, doxazosin mesylate 2mg, 3) febusostat 20mg and 4) bayaspirin 100mg, rabeprazole sodium 10mg.

Clinical progress: Nocturia has become the health problem in daily life since December 2021. He consulted with a urologist and then, he was suggested to take a diuretic. He decided not to take diuretics immediately, but to firstly check his actual situation of drinking and urinating conditions for 24 hours. After that, he investigated the detailed situation of drinking water and the state of urination for 24 hours in his lifestyle. This investigation was conducted for 2 days in Feb 2022. After that, he was advised to take furosemide 20mg at 1500h from urologist, in response to the complaint of nocturia. Similar investigation with furosemide intake was conducted for 2 days in Mar 2022.

Results

Figure 1 showed the results recorded by the subject for two days in February 2022. It is the amount and time of drinking water and urination over a 24-hour period. Among them, the drinking water volume was 750 mL/1035 mL/day, and the urine volume was 1030 mL/1400 mL/day. The ratio of urine volume during the day and night was 27%/33% during the day and 73%/67% at night. Thus, the ratio of nocturia measured during 24 hours was about 70%. The patient had to wake up twice during sleeping, and the morning urine volume was only 140mL/270mL. **Figure 2** showed the situation that furosemide 20 mg per os was taken at 1500h. Among them, the drinking water volume was 960 mL/930 mL, and the urine volume was 1090 mL/1130 mL. The ratio of urine volume during the day and night was 77%/66% during the day and 23%/34% at night. Thus, the ratio of nocturia was accounted about 30%. He did not wake up at all during all night for urination. The urine volume at the time of waking up was 360 mL/370 mL.

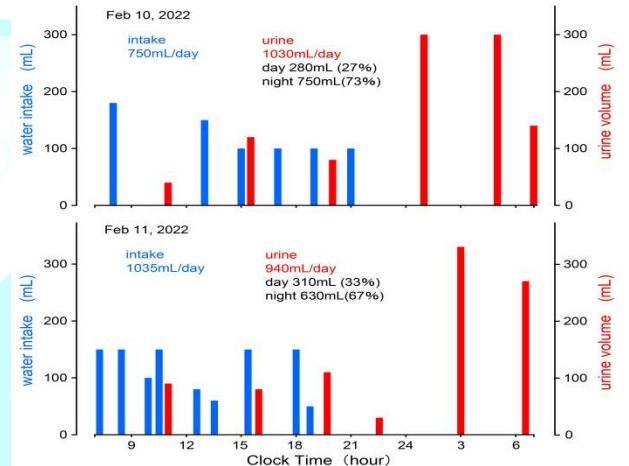


Figure 1: Results of daily water intake and urine volume in Feb 2022.

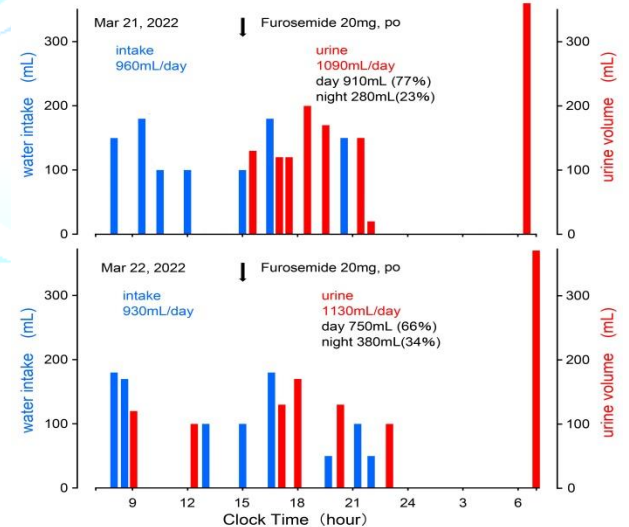


Figure 2: Results of daily water intake and urine volume with diuretic in Mar 2022.

Ethical Considerations

Current investigation was conducted along with the ethical principles which were from the Declaration of Helsinki. Further, Related comment was present for the Ethical Guidelines regarding the Research in the medical field for Human beings associated with the conduction



of the Good Clinical Practice (GCP). Authors have applied “Ethical Guidelines for Epidemiology Research” as to the related guideline. Several principles were found from the ministries of Japan, which are the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology. Regarding this subject, the written informed consent was obtained from the patient.

Discussion

In this case report, 88-year-old male complained of nocturia as a health problem. Concerning his previous history, he has had some medical problems such as hypertension, CVD, post-operative state of aortic stenosis, CKD, and diabetes. Appropriate treatment has been continued and he has been in stable condition. The case has been a chemical scientist for many years, and has previously published a paper in which 24-hour Blood Pressure (BP) measurement was tried and analyzed by himself using home BP apparatus [13]. His previous BP showed the characteristic status of higher during sleep and lower during the day. He had taken Antihypertensive Agents (AHAs) for morning and night. After analysis of daily BP profile, he was advised to take two meds at 2100h. Then his BP profile became stable during day and night.

Concerning current situation for water balance investigation, he decided to conduct the trial by himself. Various factors are involved in the problem of nocturia [17]. Among them, hypertension, AHAs, CVD, decreased cardiac function, CKD and others may be present [1]. An impressive report has been found concerning nocturia and hypertension. Meta-regression results for many reports were conducted [18]. The protocol included 25 papers from 1193 studies, using internet databases such as EMBASE, PubMed and Cochrane. As a result, overall Odds Ratio (OR) for the combination of nocturia with hypertension was 1.25 [1.21-1.28, $p < 0.001$]. This significant difference was more robust in female vs male as OR 1.45 vs 1.28, and black vs Asian vs white subgroups as 1.56 vs 1.28 vs 1.16, respectively. Unremarkable tendency was observed for body mass index or age factors. The reported evidence for diuretics was limited [18].

Regarding nocturia and AHA, systematic review was performed. The design included internet analysis of MEDLINE, PubMed, Cochrane Central in 2019, and 132 studies were investigated [19]. For calcium channel blockers, Lower Urinary Tract Symptoms (LUTS) have to be estimated before and after the intake of medicine. Thiazide diuretics have exacerbated LUTS, but Loop Diuretics Such as Furosemide (LASIX) have aggravated nocturia. Diuretics administration showed significant correlation with urination more than 3 times per night and increased rate of urinations, which is especially higher in female. For decades, nocturia has been considered as possible presence of CVD. In order to clarify the relationship between nocturia and some remarkable findings of Electrocardiogram (ECG), several biomarkers were studied such as ECG diagnosis, prolonged QTc, Left Atrial Enlargement (LAE) and Left Ventricular Hypertrophy (LVH) [20]. Studied cases were 143 patients, in which nocturia was observed for 77.6%. As a result, nocturia would predict LVH for odds ratio (OR) 2.99 and relative risk (RR) 1.18. Using the data from National Health and Nutrition Examination Survey (NHANES), the relationship of nocturia and prevalence of CVD was studied [21]. Out of 4079 patients for 7 years, 14114 cases were analyzed. Nocturia was found in 32.7% ($n=4610$), and the CVD ratio was higher in men or elder cases with smoker, higher BMI, cases with hypertension, diabetes and dyslipidemia. As a result, OR of nocturia for CVD were 1.23 (mild) and 1.74 (severe) degree, respectively.

For the relationship with nocturia and CVD, systemic review was conducted for 3524 titles and summaries [22]. Among them, 27 papers were analyzed in detail. Nocturia has found involved in several situations, including water and salt homeostasis, hypertension, hypertensive state during night, pretibial edema, B-type Natriuretic Peptide (BNP), Chronic Heart Failure (CHF) and so on. For

perspectives, adequate treatment for CVD, hypertension and CHF would be required for managing nocturia. Salt-sensitive patients with hypertension seem to excrete less salt during daytime and to excrete much salt during night. This brings more urine production as nocturia. In the case of CHF, supine position at night may lead to larger fluid volume from venous return increase from peripheral organ. Further, stretched atria and ventricles can cause stimulation of natriuretic peptide secretion [23]. Consequently, natriuresis from hypertension and hydrodiuresis from heart failure would bring nocturia. This situation can be treated by thiazide agent and loop diuretics during morning.

During the early stage of CKD, nocturia or polyuria for all day may be developed. Systematic review for nocturnal polyuria in CKD was conducted for 20 years. The protocol showed 4011 abstract and titles were screened, and among them 108 papers were fully reviewed [24]. The results showed multiple probable factors involved in nocturia, which include symptom, history, medication review, urinalysis, blood chemistry, eGFR and bladder diary. When estimating cases with nocturia, the presence of CKD would be considered for decreasing morbidity related with CKD than symptom of nocturia.

In current case, specific background has been present for his daily activity. It would be Hinohara-ism that was from Japanese supreme physician, Dr. Shigeaki Hinohara [25]. This concept enlightens the physical and mental health of the elderly [26]. This includes the common philosophy of medical care, including Dr. Schweitzer, Sir Osler, and Dr. Hinohara [27]. Hinohara-ism has brought the activities of the New elderly Association (NEA) spreading broadly for educating lots of medical professionals and general people [28]. There are five important factors, which are independence, peace, interaction, gratitude for nature, and utilizing one's own health information for research. According to the fifth element, he has actually practiced it.

Some limitation would be present in this report. This is only one case report, and such diuretic administration is not always beneficial for nocturia. Any case has different medical situation, and then we have to respond to each case. In summary, an 88-year-old patient with nocturia has studied detail status of water intake and urine volume for 24 hours by himself. By taking diuretic at 1500h, the problem was relieved. Several factors involving in this status were discussed. This report will become hopefully a reference for research and treatment of nocturia.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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