Volume 2 Issue 2, April 2020
ISSN: 2687-4245

Turkish Journal of Internal Medicine

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1. The frontline of the COVID-19 Pandemic: Healthcare Workers
2. Personal Protective Equipment Used in Coronavirus Pandemic
3. Serum Cystatin C Measurement in Lupus Nephritis Patients: Its Correlation with Clinical and Histopathological Findings
4. Effectiveness of Tolvaptan Treatment in Hyponatremic Patients
5. Herpes Zoster Ophthalmicus Infection after Kidney Transplantation
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Turkish Journal of Internal Medicine

http://www.tjim.org

e-ISSN: 2687-4245

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The journal is published quarterly (January, April, July and October)

No fee is required for publishing the manuscipt.

All articles are detected for similarity

Publisher

Turkish journal of Internal Medicine

Nizameddin KOCA

SBU Bursa Yüksek İhtisas SUAM

Yıldırm/BURSA-TURKEY

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Table of Contents

Editorial	
The frontline of the COVID-19 Pandemic: Healthcare Workers	31-32
Review	
Personal Protective Equipment Used in Coronavirus Pandemic	33-34
Original Article	
Serum Cystatin C Measurement in Lupus Nephritis Patients: Its Correlation with Clinical and Histopathological Findings	35-42
Effectiveness of Tolvaptan Treatment in Hyponatremic Patients	43-47
Case Report	
Herpes Zoster Ophthalmicus Infection after Kidney Transplantation	48-50
A Case of Pituitary Insufficiency in a Patient Presenting with Hyponatremia: Might Be Slow-Progressing Lymphocytic Hypophysitis as a Possible Cause of Empty Sella?	51-55

Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Editorial

The frontline of the COVID-19 pandemic: Healthcare workers

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Turk J Int Med 2020;2(2): 31-32
DOI: 10.46310/tjim.726917

The outbreak of Coronavirus disease 2019 (COVID-19) firstly appeared in China on December 1, 2019 and led to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread to many other countries. The World Health Organization (WHO) declared it as a pandemic on March 11, 2020. The pandemic affected approximately 3,187,952 people in the World and 225,604 people died until April 29, 2020. In the early period, many developed countries considered the COVID-19 outbreak as a simple flu epidemic. By implementing the herd immune strategy, they aimed to gain immunity by allowing a certain number of people to have mild illness and to easily control the outbreak within a few months. However, the virus spreads faster than its ancestors such as the SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV) with an estimated death rate of 2 to 3%.[1] It is still unclear how long the outbreak will last, what is the most effective treatment for the virus, and when normalization will begin. The delay in taking precautions has led to a rapid increase in the number of patients in many developed countries and a sudden collapse of healthcare capacities that cannot respond to these demands. The number of hospital beds, intensive care capacities and number of ventilators could not meet the need. For this reason, an intense and devoted period has started for healthcare professionals. Many physicians working in pandemic hospitals started to live in separate places away from their families for isolation purposes. Because the transmission rate of COVID-19 is quite higher than the flu, health care workers are at increased risk of infection, especially when performing physical examination and applying respiratory devices such as nebulizer treatments, oxygen cannulas or noninvasive ventilation.[2,3]

In this period, healthcare facilities should ensure the early recognition and isolation of possible or definite COVID-19 patients, use of recommended personal protective equipment (PPE) to minimize the staff's exposure and maintain the health workforce.[3] Most of the healthcare workers had symptoms of depression (50.4%), anxiety (44.6%), insomnia (34%) and distress (71.5%) due to the psychological stress of exposure to COVID-19.[4] Preventive strategies for all workers in a healthcare setting are warranted to reduce the risk of transmission. These measures include personal hygiene measures, such as washing hands and applying respiratory hygiene (covering coughs), using PPE, maintaining social distance and avoiding crowds and, if possible, close contact with ill individuals. Despite all precautions, in China, more than 3,300 healthcare workers were infected (4% of the 81,285 reported infections). In Spain, nearly 6,500 (13.6%) medical personnel were infected among 47,600 total cases until March 25, 2020 and this was 1% of the health system's workforce.[5] In Italy, 9% of Italy's COVID-19 cases was healthcare workers. The rate of infections among nurses and other healthcare staff is higher.[6] In Italy, France and Spain, more than 30 healthcare workers have died of the COVID-19.[7]

Received: April 17, 2020; Accepted: April 26, 2020; Published Online: April 29, 2020
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According to unofficial information, the Turkish Medical Association (TTB) reported that 3,474 healthcare workers, 38% of which were physicians, were diagnosed with COVID-19.[8]

Healthcare workers were expected to comply with these measures in all areas that are contaminated (pandemic) and decontaminated. In a China study, medical personnel working on the COVID-19 front lines had a lower frequency of burnout (13% vs. 39%) and less worried about being infected when compared to medical personnel working on their usual wards for uninfected patients.[9] Contrary, frontline health care workers showed a higher risk of symptoms of depression 1.52-fold, anxiety 1.57-fold, insomnia 2.97-fold and distress 1.60-fold in another survey study.[4] As there are many asymptomatic carriers, healthcare workers are very likely to become infected inside and outside the hospital. However, it is noteworthy that healthcare workers other than doctors and nurses sometimes do not show the same concentration in common areas and may violate the rule of maintaining social distance. The risk of transmission of these latter employees were observed to be mostly caused by non-hospital contacts. The increase in the number of infected healthcare workers has increased the workload of the rest. Because thousands of healthcare workers who are infected have to self-isolate themselves, they have to stay away from work for at least 14 days which depletes the already exhausted workforce.[6] Currently, Turkish health minister declared that the number of healthcare workers infected with COVID-19 until today was 7,428 in Turkey, which was approximately 6.5% of all infected individuals in the country.

The first case in our country was seen on March 11, 2020, and the number of cases increased gradually in the following days. The Ministry of Health and Science Committee prepared the national COVID-19 guidelines, successfully managed the whole process from the beginning and continues to take the necessary measures to prevent the spread of the outbreak. In our country, the number of hospital capacity, intensive care units, ventilators and health personnel seems sufficient. However, the most important task here is still on health professionals. Healthcare professionals have three important tasks: treating patients, protecting themselves from contamination, and finally not infecting their patients, families and friends with COVID-19. Awareness of not only doctors and nurses but also all hospital staff should be kept in high concentration until vaccine or effective treatment is found or the outbreak is controlled.

Conflict of interest

The author declared that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References

1. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020 Apr;87(4):281-286. doi: 10.1007/s12098-020-03263-6.
2. Ferioli M, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. Eur Respir Rev. 2020 Apr 3;29(155). pii: 200068. doi: 10.1183/16000617.0068-2020.
3. Heinzerling A, Stuckey MJ, Scheuer T, Xu K, Perkins KM, Resseger H, Magill S, Verani JR, Jain S, Acosta M, Epson E. Transmission of COVID-19 to Health Care Personnel During Exposures to a Hospitalized Patient - Solano County, California, February 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 17;69(15):472-476. doi: 10.15585/mmwr.mm6915e5.
4. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, Wu J, Du H, Chen T, Li R, Tan H, Kang L, Yao L, Huang M, Wang H, Wang G, Liu Z, Hu S. Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open. 2020 Mar 2;3(3):e203976. doi: 10.1001/jamanetworkopen.2020.3976.
5. Heneghan C, Oke J, Jefferson T. COVID-19 How many Healthcare workers are infected? April 17, 2020. Available from: https://www.cebm.net/covid-19/covid-19-how-many-healthcare-workers-are-infected/. (cited Apr 2020).
6. International Council of Nurses. Available from: https://www.icn.ch/news/high-proportion-healthcare-workers-covid-19-italy-stark-warning-world-protecting-nurses-and. (cited Apr 2020).
7. Available from: https://www.nytimes.com/2020/03/24/world/europe/coronavirus-europe-covid-19.html. (cited Apr 2020).
8. Türk Tabipleri Birliği (TTB) Merkez Konseyi. 22.04.2020. Available from: https://www.ttb.org.tr/kollar/COVID19/haber_goster.php?Guid=e344765a-846e-11ea-9137-e385f12afb6d. (cited Apr 2020).
9. Wu Y, Wang J, Luo C, Hu S, Lin X, Anderson AE, Bruera E, Yang X, Wei S, Qian Y. A comparison of burnout frequency among oncology physicians and nurses working on the front lines and usual wards during the COVID-19 epidemic in Wuhan, China. J Pain Symptom Manage. 2020 Apr 10. pii: S0885-3924(20)30205-0. doi: 10.1016/j.jpainsymman.2020.04.008.

Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Review

Personal Protective Equipment used in Coronavirus Pandemic

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Turk J Int Med 2020;2(2): 33-34
DOI: 10.46310/tjim.726489

Cases of pneumonia of unknown etiology in Wuhan, China's Hubei province, was reported to the China country Office of the World Health Organization (WHO) on December 31, 2019. The causative agent was identified as a new coronavirus (2019-nCoV) on January 7, 2020 that has not previously been detected in humans. Later, the name of 2019-nCoV disease was accepted as COVID-19, and the virus was named as SARS-CoV-2 due to its similarity to SARS CoV.[1-3]

During the SARS-CoV-2 pandemic period, special attention should be paid to personal protective equipment (PPE). Medical staff protection is particularly important because of the risk of infecting other medical team members, not only doctors, nurses or paramedics, but also other support staff necessary to ensure continuity of care for patients.[4,5]

It is important for the healthcare professionals working in triage to wear a medical mask and provide at least 1-meter distance to the patients and give a medical mask to the patients who apply to triage without wearing a mask. Laboratory workers are required to wear medical masks, gowns, gloves while working with breathing samples and glasses / face shields during operations with the risk of splashing.

Health personnel working in the outpatient clinic should use PPE according to standard measures and risk assessment. During the examination of the patient with respiratory symptoms, a medical mask, gowns, gloves, glasses / face shields should be used, and during the examination of patients without respiratory symptoms, the patient should wear a medical mask.

In emergency departments, it is recommended to use N95 or FFP2 or equivalent masks, gloves, glasses / face shields and gowns during the examination of patients referred to COVID emergency clinics in reserved area for the examination of possible coronavirus cases. Also, healthcare professionals working in sampling units designated in these areas should consider all samples taken as potentially infectious, sampling should be considered as the process that causes aerosolization, and individuals should have personal protective equipment (at least N95 / FFP2 mask, glasses or face protection).[6]

It is recommended that the healthcare personnel entering the patient room should use medical masks, gowns, gloves, glasses / face shields, and use N95, FFP2 or equivalent mask during aerosol-forming procedures. When entering the patient room, cleaning staff are recommended to wear medical masks, gowns, gloves, glasses and to use face shield if there is a risk of organic or chemical material splash.

Under normal conditions, visitors are not allowed in the patient room. If it is necessary to enter the COVID-19 patient room, they should be informed and supervised by a healthcare professional about wearing a medical mask, gowns, and gloves, before and after wearing PPE.[6]

Despite many innovations in infection control

Received: April 24, 2020; Accepted: April 26, 2020; Published Online: April 29, 2020
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and prevention in hospitals, tuberculosis, multidrug-resistant bacteria, SARS CoV in 2003, MERS CoV in 2012 and COVID-19 pandemics that emerged this year have once again have shown us that hand hygiene and isolation precautions are very important. The main purpose in isolation is to prevent the transmission of microorganisms from infected or colonized patients to other patients, patient visitors and health personnel.[7]

Isolation can be grouped under two headings as standard precautions and precautions for transmission. Standard precautions are measures applied to all patients regardless of the patient's diagnosis and whether they have an infection. In the care of all patients, they are the first precautions to be applied against blood, body fluids and extracts. The basis of these is the cleaning and the use of appropriate barriers that will prevent the contact with the risky material. Before contact with contaminated material (blood, body fluids, secretions other than sweat and all extracts, impaired skin and mucous membranes, contaminated items ...); gloves, masks and protective gowns are worn and if it is necessary, eye protection (glasses or face shield) should be made in case of droplet formation risk. Gloves must be removed, and hands washed before touching clean items or another patient.[8]

Contact and droplet isolation is important in COVID patients in the prevention for transmission. Contact precautions should be applied in addition to standard precautions to prevent direct or indirect contact (contact with infected objects) from patients infected or colonized samples.[7,8]

It should be applied in addition to standard measures to prevent the passage of large particle (> 5 μm) droplets. There should be more than 1-meter distance between the source and the sensitive person to avoid contamination. Speaking, coughing or nasal wiping, aspiration, intubation, bronchoscopy of infected patients may infect the susceptible person through the nose, mouth and conjunctiva. When a condition requiring droplet isolation is detected or suspected, the patient should be placed in a single room. Access to the patient room should be restricted, only personnel responsible for the patient's care and required access should be allowed to enter the room, patient visitors should be banned, and the companion should be restricted to one person if necessary. At the entrance of the patient room; personal protective materials (gloves, gowns (non-sterile, preferably liquid impermeable and long sleeve), medical mask, at least N95 / FFP2 mask, glasses / face shields, alcohol-based hand antiseptics and alcohol-based rapid surface disinfectant) should be ready. People who make examination, treatment and personal care should wear gloves, isolation gowns, glasses / face shields, and medical masks. Care should be taken to use gloves, isolation gowns, N95 / FFP2 mask and face shields when attempting to cause aerosolization of the patient's secretions and the body fluids.[6-8]

Conflict of interest

The author declared that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References

1. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-theyhappen. [cited 2020 Apr].
2. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020 Apr;26(4):450-452. doi: 10.1038/s41591-020-0820-9.
3. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü, COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi, Bilim Kurulu Çalışması. Ankara: T.C. Sağlık Bakanlığı; 14.04.2020: 1-95. Available from: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf. [cited 2020 Apr].
4. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anaesth. 2020 May;67(5):568-576. doi: 10.1007/s12630-020-01591-x.
5. Smereka J, Szarpak L. COVID 19 a challenge for emergency medicine and every health care professional. Am J Emerg Med. 2020 Mar 24. pii: S0735-6757(20)30180-7. doi: 10.1016/j.ajem.2020.03.038.
6. T.C. Sağlık Bakanlığı. COVID-19 Hastalığına Yönelik Sağlık Kuruluşu, Personel Ve Faaliyet Türüne Göre Kullanılması Önerilen Koruyucu Ekipmanlar. T.C Sağlık Bakanlığı Halk Sağlığı Başkanlığı Dökümanı. Ankara: https://covid19bilgi.saglik.gov.tr/depo/enfeksiyon-kontorl-onlemleri/KISISEL_KORUYUCU_EKIPMAN_KULLANIMI.pdf. [cited 2020 Apr].
7. Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Last update: July 2019: 1-206. Available from: https://www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines-H.pdf. [cited 2020 Apr].
8. World Health Organization Scientific brief. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. 29.03.2020. Available from: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. [cited 2020 Apr].

Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Original Article

Serum Cystatin C Measurement in Lupus Nephritis Patients: Its Correlation with Clinical and Histopathological Findings

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Abstract

Introduction. To investigate the relationship between serum cystatin C levels and disease activity, renal function test, and histopathological findings in patients with lupus nephritis that did not receive any previous treatment.
Methods. 20 patients with lupus nephritis and 20 healthy subjects were included in the study. Before initiation of spesific treatment, clinical and laboratory findings including serum creatinine, cystatin C, daily proteinuria and Cockcroft and Gault (C-G) and Modification of Diet in Renal Disease (MDRD) study equation in adults creatinine clearances (CrCl), as well as histopathological activity and chronicity indices and systemic lupus erythematosus disease activity index (SLEDAI) were evaluated.
Results.Serum creatinine, cystatin C, C-G and MDRD CrCls in the patients with lupus nephritis and controls were comparable. Both serum creatinine and cystatin C levels positively correlated with activity index and SLEDAI. There was a negative correlation between C-G CrCl with activity index and MDRD CrCl with activity index and SLEDAI.
Conclusions.Our findings suggest that in lupus nephritis measuring the cystatin C level before renal biopsy is performed can not provide a more beneficial predictor than creatinine.

Turk J Int Med 2020;2(2): 35-42
DOI: 10.46310/tjim.710052

Keywords: Creatinine clearance, creatinine, cystatin C, systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause which can affect the skin, joints, kidneys, lungs, nervous system, serous membranes and/or other organs of the body. Renal involvement in SLE is a common manifestation and a story predictor of poor outcome.[1,2] Renal biopsy plays an important role in the diagnosis and staging of lupus nephritis It also guides the appropriate selection of treatment especially for high-risk patients.[3] Glomerular dysfunction is usually more prominent and clinically important than tubular dysfunction in

Received: March 31, 2020; Accepted: April 28, 2020; Published Online: April 29, 2020

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lupus nephritis. Ideally, glomerular filtration rate (GFR) should be determined with a method that is convenient, inexpensive, and accurate. Serum creatinine is the most widely used screening test to detect abnormalities of glomerular filtration.[4] It is affected not only by GFR, but also by age and muscle mass.[5] GFR can be estimated from serum creatinine using Modification of Diet in Renal Disease (MDRD) or Cockroft and Gault (C-G) equations.[5,6] However, these equations have not been generalizable across all clinical presentation. For example, the MDRD equation, derived with chronic kidney disease patients, underestimated GFR in healthy persons by 29%.[7] All methods for estimating GFR have their strengths and limitations.

Human cystatin C is a 132-amino-acid, 13-kd cysteine protease inhibitor, which is produced by all nucleated cells and modulated by intracellular protein catabolism. Its endogenous production rate is unaltered during inflammatory processes.[8] Serum cystatin C reliably detects renal dysfunction in patients with various renal disease including SLE.[9,10] Cystatin C is a biomarker with significant advantages over serum creatinine in patients with extremes in muscle mass, weight, age, and other areas where estimating equations using creatinine have well documented limitations.[11] Available data on cystatin C in lupus nephritis are limited-. There are few studies investigating the relationship of new kidney biomarkers with disease activity and damage in lupus nephritis.[12-16] The aim of this study was to investigate the relationship between serum cystatin C levels with disease activity, other renal function tests, clinical and histopathological findings in patients with lupus nephritis who did not receive any previous treatment.

Methods

Patients hospitalized in our clinic between 1999 and 2003 with newly diagnosed SLE not being treated with corticosteroids and/or immunosuppressive therapy, were analyzed. Patients with bleeding diathesis, single kidney, acute urinary infection or rapidly progressive glomerulonephritis were excluded from the study. The study was performed in accordance with the Helsinki Human Rights protocol. Written informed consents were obtained from all patients.

SLE was diagnosed according to the 1982 classification criteria of SLE by the American College of Rheumatology (ACR).[17] A total of 20 caucasion SLE cases who had proteinuria or/and hematuria were included in the study. Control subjects were derived from our internal medicine outpatient clinics and twenty healthy individuals evaluated. All control subjects underwent a detailed examination and they had normal findings.

Before the initiation of treatment, complete urine analysis, daily urine protein excretion, whole blood count, coagulation tests, erythrocyte sedimentation rate, serum urea, creatinine, electrolytes, total protein, albumin, AST and ALT levels, serum protein electrophoresis, C-reactive protein (CRP), immunoglobulin levels, anti-nuclear antibody (ANA), anti-double-strain DNA (anti-dsDNA), complement (C) 3 and C4 were measured for all patients.

Percutaneous renal biopsy was performed to these patients using a 14-16 G Magnum bard biopsy needle guided with ultrasonography. Presence of 10 glomeruli and 2 vessels in the biopsy materials was considered as sufficient material. Biopsy materials were treated with hematoxylin-eozin (HE), periodical acid-Schiff (PAS), Masson Trichromium (MT), periodical acid silver methenamine (PAS-M) dyes. All biopsies were evaluated by light microscopy and immunofluorescence. According to the International Society of Nephrology/Renal Pathology Society Classification (ISN/RPS) 2003 histopathological classification, there were mesangial proliferative lupus nephritis in 6 patients (Class II), focal lupus nephritis in 6 patients (Class III), diffuse lupus nephritis in 6 patients (Class IV) and membranous lupus nephritis in 2 patients (Class V).[18,19] Then, each biopsy was calculated for activity and chronicity indices using a semi quantitative ranking system.[20,21] In these indices glomerular and tubulointerstitial lesions were ranked as 0 (no lesions), 1, 2 or 3 (+) semi quantitatively. As activity indices glomerular hypercellularity, leukocyte exudation, karyorrhexis, fibrinoid necrosis, cellular crescent, hyaline collection and interstitial cellular infiltration was evaluated. The total score was determined using a 24 point scale. For chronicity indices glomerular sclerosis, fibrous crescent, tubular atrophy and interstitial fibrosis were evaluated. The total score was determined

using a 12 point scale.

The SLE disease activity index (SLEDAI) was also determined from the clinical and laboratory data of these cases. Psychosis, organic brain syndrome, findings associated with vision, cranial nerve damage, lupus headache, paralysis and presence of vasculitis 8 points each; arthritis, myositis, cast, proteinuria and pyuria 4 points each; new malar rash, alopecia, mucosal lesions, pleurisy, pericarditis, reduced complement and increased anti-dsDNA 2 points each; and fever, thrombocytopenia, leucopenia were assigned 1 point each.[22]

Creatinine clearance (CrCl) was calculated with C-G [(140- age) (body weight in kg) / 72 x serum creatinine (mg/dL) (0.85 if patient was female)][6] and MDRD [186 x [serum creatinine (mg/dL)]$^{-1.154}$ x [age]$^{-0.203}$ x (0.742 if patient was female)][5] prediction equation for adults formulas. Serum samples taken before biopsies were kept at – 55 °C in a deep freezer. Serum cystatin C levels were measured in a BNII nephelometer (Dade Behring Inc, Germany) using a particle-enhanced immunonepholometric assay (N Latex Cystatin-C). Normal ranges for male and female were 0.57 to 0.96 mg/L and 0.50 to 0.96 mg/L, respectively.

All statistical analysis was done with statistical programme of SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Clinical and laboratory data were expressed as mean± SD. By taking variability skewness (a3) and curtosis (a4) values into account the non-parametric and parametric test options were evaluated. The numerical variables of patients with lupus nephritis and controls were compared with unpaired student t test or Mann-Whitney U test. For comparisons of ratios in both groups, Fisher exact test was used. Correlations between numerical variables were tested by the Pearson rank correlation test (r = correlation coefficient). $p<0.05$ was considered statistically significant.

Results

The age, gender distribution, serum creatinine, cystatin C and C-G and MDRD CrCls in the patients with lupus nephritis and controls were similar ($p>0.05$, Table 1). 12 patients (60%) had malar rash, 7 (35%) discoid rash, 7 (35%) photosensitivity, 6 (30%) oral ulcers, 9 (45%) arthropathy, 2 (10%) serositis, 1 (5%) neurological, 8 (40%) hematological disorder, 20 (100%) renal disorder, 16 (80%) immunologic disorder and 18 (90%) abnormal titer of ANA. In all patients with lupus nephritis, CRP levels were 0.86 mg/dL (range: 0.5-3.8), activity indices 6.1 (0-16), chronicity indices 0.7 (0-3) and SLEDAI 14.7 (5-30). The correlation analysis between all parameters of 20 lupus nephritis patients was performed (Table 2).

The serum creatinine values negatively correlated with C-G and MDRD CrCls and positively correlated with cystatin C (Figure 1a), activity indices and SLEDAI. There was a positive relationship between serum cystatin C with activity index (Figure 1b) and SLEDAI (Figure 1c), but not C-G and MDRD CrCls. There was a negative correlation between C-G CrCl with activity index and MDRD CrCl with

Table 1. The comparison of demographic features and renal function parameters in patients with lupus nephritis and controls*

	Lupus nephritis (n:20)	Control (n:20)
Age (year)	32.6 ± 11.1	29.5 ± 7.3
Gender (male/female)	2/18	2/18
BMI (kg/m^2)	23.0 ± 3.4	23.1 ± 4.3
Creatinine (mg/dL)	0.85 ± 0.3	0.79 ± 0.1
Cystatin C (mg/L)	0.97 ± 0.5	0.76 ± 0.08
C-G CrCl (mL/min)	100.1 ± 31	112 ± 35
MDRD CrCl (mL/min)	93 ± 28	109 ± 29

BMI: body mass index, CrCl: creatinine clearence, C-G: Cockcroft and Gault, MDRD: Modification of Diet in Renal Disease study equation in adults. * $p>0.05$

Table 2. The correlations of clinical and histopathological findings with renal function parameters in the lupus nephritis patients

		Cystatin C	C-G CrCl	MDRD CrCl	Activity Index	Chronicity index	SLEDAI
Creatinine	r	0.686	-0.792	-0.827	0.547	0.029	0.526
	p	0.001	0.001	0.001	0.013	0.902	0.017
Cystatin C	r		-0.434	-0.387	0.459	0.028	0.489
	p		0.056	0.09	0.042	0.907	0.029
C-G CrCl	r			0.876	-0.573	0.085	-0.309
	p			0.001	0.008	0.721	0.186
MDRD CrCl	r				-0.497	0.155	0.457
	p				0.026	0.515	0.043

CrCl: creatinine clearance, C-G: Cockcroft and Gault, MDRD: Modification of Diet in Renal Disease study equation in adults, SLEDAI: Systemic lupus erythematosus disease activity index.

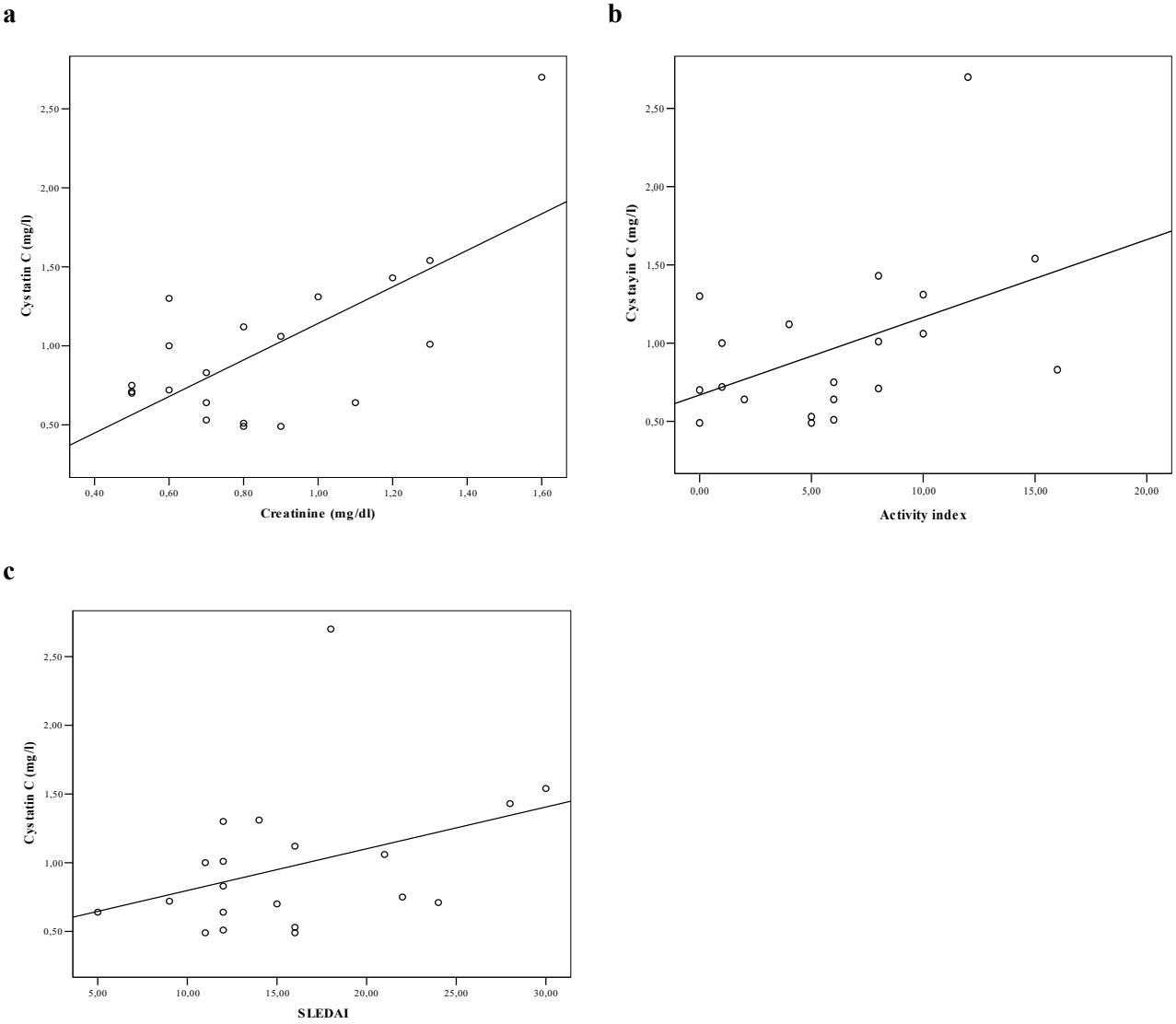

Figure 1. Correlations between serum Cystatin C with creatinine (a) activity index (b) and SLEDAI (c) in the patients with lupus nephritis

activity index and SLEDAI. These renal functions parameters did not correlate with CRP levels and daily protein excretions.

Discussion

There is a strong correlation between serum creatinine and cystatin C. Cystatin C has been proposed as an indicator of GFR with a higher diagnostic efficacy than serum creatinine.[23,24] Its concentration appears to be independent of gender, age, nutrition, medications or body mass.[25,26] However, in at least one general population study, cystatin C was found to be influenced by several factors age, gender body size and cigarette smoking independent from CrCl.[27] Recent studies have shown that serum cystatin C can be used as an accurate marker of GFR in diabetic and nondiabetic patients.[9,10,23] However, C-G CrCl remained the best marker of renal function in diabetic patients when compared Cr-EDTA and other parameters such as cystatin C and creatinine.[10] A large number of studies favor cystatin C over serum creatinine for estimation of GFR, but not all.[28]

A study that was performed in 226 patients with various nephropaties except SLE showed that serum cystatin C was at least as efficacous as serum creatinine in detecting a reduced GFR as measured by CrCl.[29] Serum cystatin C levels were found to be higher in SLE patients than in healthy controls and in SLE patients with a history of lupus nephritis than those without a history of nephritis. In the same study, serum cystatin C correlated positively with serum creatinine, and inversely to renal measures such as the modified C-G and MDRD equations. In the multivariate analysis, age, serum creatinine and high-sensitivity CRP was independently associated with serum cystatin C.[30] Reciprocal of serum cystatin C also was well correlated with GFR obtained by the standard sodium thiosulfate clearance test [C(Thio)]. A study of 212 patients with various renal diseases all histopathologically proven by renal biopsy showed that no factors other than C(Thio) affected serum cystatin C concentrations, whereas age, SLE, dosage of daily prednisolone and CRP affected beta2-microglobulin concentrations, and both gender and dosage of daily prednisolone affected serum creatinine concentrations.[9] It is unclear whether glucocorticoid therapy affects serum cystatin C levels in lupus nephritis patients. The recent study have not observed such interference in the lupus nephritis patients submitted to corticotherapy.[31] The measurements of our patients with SLE were taken at the time of diagnosis before specific treatment was initiated.

One of the main purposes of GFR estimation in clinical practice is to screen for patients with mild renal disfunction. A recent study in patients with different stages of chronic kidney disease indicated that serum cystatin C was reliable marker of GFR in patients with decreased GFR.[32] Serum cystatin C was find more efficacious than serum creatinine and CrCl in detecting reduced GFR in type 2 diabetes patients.[33] The serum cystatin C concentrations can be determined from a single blood sample making this parameter a reliable screening measure for identifying patients with subclinical renal failure. Tomino et al.[34] showed that the level of serum cystatin C were statistically correlated with the prognostic stages of patients with IgA nephropathy prior to renal biopsy in contrast with serum creatinine and CrCl. The present study did not suggest that cystatin C could be more useful to detect impaired renal function in lupus nephritis, although the size of lupus nephritis groups were too small to make any definite conclusion. Indeed, the use of serum creatinine-based equations rather than GFR as the gold standart in this study limits its conclusions. Also we did not compare the renal function parameters of patients in different stages due to the small number of patients we studied in each class. In a large case-control study including 334 patients with active lupus nephritis, 255 patients with inactive lupus nephritis and 497 healthy individuals, estimated GFR cystatin-C (MDRD) and C1q were superior to the conventional biomarkers urea, creatinine and estimated GFR creatinine in the diagnosis of active lupus nephritis.[35] Although beta 2-microglobulin/serum creatinine index is a prognostic factor predicting active lupus, beta 2-microglobulin/cystatin C index has no added benefit in the assessment of renal activity in SLE.[36]

Although the aforementioned studies have tested the correlation between serum cystatin C and other renal function tests, most of these studies have not evaluated the relationship of renal markers with clinical and histapatological activity findings in patients with lupus nephritis. We studied

the correlation between renal function tests with SLEDAI and histapathological activity indices. Serum cystatin C, creatinine and CrCl equations correlated with activity indices and SLEDAI (except C-G CrCl), but not chronicity indices. Confounding factors associated with cystatin C could lead to inaccurate GFR estimations in lupus nephritis patients. A recent study showed 19% higher GFR at the same cystatin C level among kidney transplant recipients compared to native kidney disease patients.[37] They suggested that the responsible mechanism could be increased cystatin C production from systemic inflammation or use of immunosuppression therapy in this population. Kidney dysfunction is known to be associated with elevations in inflammatory biomarkers. Knight et al.[27] found that cystatin C was associated with CRP even after adjustment for CrCl, implying that the protein cystatin C had some biologic link to inflammation. A recent study found that CRP and fibrinogen levels were linearly associated with quintiles of cystatin C in elderly.[38] In our study cystatin C levels did not correlate with CRP levels in our untreated newly diagnosed lupus nephritis patients. SLE could influence serum cystatin C, but its levels were comparable patients with lupus nephritis and healthy subjects. It has been reported associations between anti-CRP and and histopathological activity or disease activity in lupus nephritis.[39]

The results of recent studies on new serum and urine biomarkers in patients with SLE are promising. Among all urinary markers, urinary clusterin is better marker at predicting end-stage renal disease than others (albumin, beta 2-microglobulin, cystatin C, kidney injury molecule-1, monocyte chemoattractant protein-1, calbindin, interleukin-18, neutrophil gelatinase-associated lipocalin, trefoil factor 3, osteopontin, and glutathione S-transferase). Interestingly, elevation of urinary clusterin likely resulted from local over-expression in tubulointerstitial tissue.[40] In other study, novel urinary cytokines and chemokines (urinary monocyte chemoattractant protein 1 and tumor necrosis factor-like weak inducer of apoptosis) possess higher correlation coefficients with renal damage than traditional serum or urinary markers (urinary alpha 1-microgrobulin, beta 2-microglobulin and serum C3, C4, creatinine, blood urea nitrogen and cystatin C) in lupus nephritis.[41] There was a significant increase in serum cystatin C, urinary neutrophil gelatinase-associated lipocalin (UNGAL) and N-acetyl-beta-D-glucosaminidase (UNAG) levels in adult SLE patients compared with controls. Serum cystatin C significantly correlated with the damage index, renal biopsy class and negatively with the serum albumin; UNGAL correlated with albuminuria and the level of nephritis and UNAG negatively correlated with serum albumin level.[42]

Conclusions

Cystatin C is an important endogenous filtration marker that is being considered as a potential replacement for serum creatinine. Measurement of serum cystatin C level other than creatinine before renal biopsy in lupus nephritis patients did not provide more advantage for the prediction of histopathological activity index as well as SLEDAI. However, it is currently more expensive to measure cystatin C than creatinine, so it is not widely used as a GFR marker in most of the countries. Further prospective studies should focus on whether serum cystatin C correlates with longterm renal outcome better than chemical methods for assessing kidney function in patients with various renal diseases including SLE.

Acknowledgement

The authors dedicated this article to the memory of our colleague, Dr. Gulaydan Filiz, who also evaluated the pathological findings of this study and lost at the most productive age.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman Tahir H, Isenberg DA. Novel therapies in lupus nephritis. Lupus. 2005;14(1):77-82.
2. Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology (Oxford). 2011 Aug;50(8):1424-30. doi: 10.1093/rheumatology/ker101.
3. Mittal B, Rennke H, Singh AK. The role of kidney biopsy in the management of lupus nephritis. Curr Opin Nephrol Hypertens. 2005 Jan;14(1):1-8.
4. Balow JE. Clinical presentation and monitoring of lupus

nephritis. Lupus. 2005;14(1):25-30.
5. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003 Jul 15;139(2):137-47.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
7. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med. 2004 Dec 21;141(12):929-37.
8. Hermida J, Romero R, Tutor JC. Relationship between serum cystatin C and creatinine in kidney and liver transplant patients. Clin Chim Acta. 2002 Feb;316(1-2):165-70.
9. Kazama JJ, Kutsuwada K, Ataka K, Maruyama H, Gejyo F. Serum cystatin C reliably detects renal dysfunction in patients with various renal diseases. Nephron. 2002 May;91(1):13-20.
10. Perlemoine C, Beauvieux MC, Rigalleau V, Baillet L, Barthes N, Derache P, Gin H. Interest of cystatin C in screening diabetic patients for early impairment of renal function. Metabolism. 2003 Oct;52(10):1258-64.
11. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens. 2015 May;24(3):295-300. doi: 10.1097/MNH.0000000000000115.
12. Madureira Silva MV, Moscoso-Solorzano GT, Nishida SK, Mastroianni-Kirsztajn G. Serum Beta 2-microglobulin/cystatin C index: a useful biomarker in lupus nephritis? Nephron Extra. 2012 Jan;2(1):169-76. doi: 10.1159/000339643.
13. Chew C, Pemberton PW, Husain AA, Haque S, Bruce IN. Serum cystatin C is independently associated with renal impairment and high sensitivity C-reactive protein in systemic lupus erythematosus. Clin Exp Rheumatol. 2013 Mar-Apr;31(2):251-5.
14. Gheita TA, Abd El Baky AM, Assal HS, Farid TM, Rasheed IA, Thabet EH. Serum cystatin C, urinary neutrophil gelatinase-associated lipocalin and N-acetyl-beta-D-glucosaminidase in juvenile and adult patients with systemic lupus erythematosus: Correlation with clinical manifestations, disease activity and damage. Saudi J Kidney Dis Transpl. 2015 May-Jun;26(3):497-506. doi: 10.4103/1319-2442.157336.
15. Dong XW, Zheng ZH, Ding J, Luo X, Li ZQ, Li Y, Rong MY, Fu YL, Shi JH, Yu LC, Wu ZB, Zhu P. Combined detection of uMCP-1 and uTWEAK for rapid discrimination of severe lupus nephritis. Lupus. 2018 May;27(6):971-981. doi: 10.1177/0961203318758507.
16. Xu B, Zhang YM, Yang YW, Liu YS, Feng JF. Diagnostic performance of serum cystatin C and complement component 1q in lupus nephritis. Arthritis Res Ther. 2019 Dec 4;21(1):267. doi: 10.1186/s13075-019-2065-x.
17. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982 Nov;25(11):1271-7.
18. Chan TM. Histological reclassification of lupus nephritis. Curr Opin Nephrol Hypertens. 2005 Nov;14(6):561-6.
19. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB, Ginzler EM, Hebert L, Hill G, Hill P, Jennette JC, Kong NC, Lesavre P, Lockshin M, Looi LM, Makino H, Moura LA, Nagata M. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004 Feb;15(2):241-50.
20. Churg J, Bernstein J, Glassock RJ. Lupus nephritis. In: Churg J, Bernstein J, Glassock RJ, eds. Renal Diseases: Classification and Atlas of Glomerular Diseases. 2nd Ed. New York: Igaku-Shoin; 1995:151-6.
21. Austin HA 3rd, Muenz LR, Joyce KM, Antonovych TA, Kullick ME, Klippel JH, Decker JL, Balow JE. Prognostic factors in lupus nephritis. Contribution of renal histologic data. Am J Med. 1983 Sep;75(3):382-91.
22. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 1992 Jun;35(6):630-40.
23. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW. Biological variation of cystatin C: implications for the assessment of glomerular filtration rate. Clin Chem. 1998 Jul;44(7):1535-9.
24. Massey D. Commentary: clinical diagnostic use of cystatin C. J Clin Lab Anal. 2004;18(1):55-60.
25. Finney H, Newman DJ, Price CP. Adult reference ranges for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem. 2000 Jan;37 (Pt 1):49-59.
26. Vinge E, Lindergård B, Nilsson-Ehle P, Grubb A. Relationships among serum cystatin C, serum creatinine, lean tissue mass and glomerular filtration rate in healthy adults. Scand J Clin Lab Invest. 1999 Dec;59(8):587-92.
27. Knight EL, Verhave JC, Spiegelman D, Hillege HL, de Zeeuw D, Curhan GC, de Jong PE. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int. 2004 Apr;65(4):1416-21.
28. Zahran A, El-Husseini A, Shoker A. Can cystatin C replace creatinine to estimate glomerular filtration rate? A literature review. Am J Nephrol. 2007;27(2):197-205.
29. Herget-Rosenthal S, Trabold S, Pietruck F, Holtmann M, Philipp T, Kribben A. Cystatin C: efficacy as screening test for reduced glomerular filtration rate. Am J Nephrol. 2000 Mar-Apr;20(2):97-102.
30. Chew C, Pemberton PW, Husain AA, Haque S, Bruce IN. Serum cystatin C is independently associated with renal impairment and high sensitivity C-reactive protein in systemic lupus erythematosus. Clin Exp Rheumatol. 2013 Mar-Apr;31(2):251-5.
31. Silva MV, Moscoso Solorzano G, Nishida SK, Kirsztajn GM. Are serum cystatin C levels influenced by steroid doses in lupus nephritis patients? J Bras Nefrol. 2011 Jul-Sep;33(3):306-12.
32. Hojs R, Bevc S, Ekart R, Gorenjak M, Puklavec L. Serum cystatin C as an endogenous marker of renal function in patients with chronic kidney disease. Ren Fail. 2008;30(2):181-6. doi: 10.1080/08860220701810315.
33. Xia LH, Bing XG, An XT. Serum cystatin C assay for the detection of early renal impairment in diabetic patients. J Clin Lab Anal. 2004;18(1):31-5.
34. Tomino Y, Suzuki S, Gohda T, Kobayashi M, Horikoshi S, Imai H, Saito T, Kawamura T, Yorioka N, Harada T, Yasumoto Y, Kida H, Kobayashi Y, Endoh M, Sato H, Saito K. Serum cystatin C may predict the prognostic

stages of patients with IgA nephropathy prior to renal biopsy. J Clin Lab Anal. 2001;15(1):25-9.
35. Xu B, Zhang YM, Yang YW, Liu YS, Feng JF. Diagnostic performance of serum cystatin C and complement component 1q in lupus nephritis. Arthritis Res Ther. 2019 Dec 4;21(1):267. doi: 10.1186/s13075-019-2065-x.
36. Madureira Silva MV, Moscoso-Solorzano GT, Nishida SK, Mastroianni-Kirsztajn G. Serum Beta 2-microglobulin/cystatin C index: a useful biomarker in lupus nephritis? Nephron Extra. 2012 Jan;2(1):169-76. doi: 10.1159/000339643.
37. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. Kidney Int. 2006 Jan;69(2):399-405.
38. Shlipak MG, Katz R, Cushman M, Sarnak MJ, Stehman-Breen C, Psaty BM, Siscovick D, Tracy RP, Newman A, Fried L. Cystatin-C and inflammatory markers in the ambulatory elderly. Am J Med. 2005 Dec;118(12):1416.
39. Sjöwall C, Zickert A, Skogh T, Wetterö J, Gunnarsson I. Serum levels of autoantibodies against C-reactive protein correlate with renal disease activity and response to therapy in lupus nephritis. Arthritis Res Ther. 2009;11(6):R188. doi: 10.1186/ar2880.
40. Wu CY, Yang HY, Chien HP, Tseng MH, Huang JL. Urinary clusterin-a novel urinary biomarker associated with pediatric lupus renal histopathologic features and renal survival. Pediatr Nephrol. 2018 Jul;33(7):1189-1198. doi: 10.1007/s00467-018-3924-4.
41. Dong XW, Zheng ZH, Ding J, Luo X, Li ZQ, Li Y, Rong MY, Fu YL, Shi JH, Yu LC, Wu ZB, Zhu P. Combined detection of uMCP-1 and uTWEAK for rapid discrimination of severe lupus nephritis. Lupus. 2018 May;27(6):971-981. doi: 10.1177/0961203318758507.
42. Gheita TA, Abd El Baky AM, Assal HS, Farid TM, Rasheed IA, Thabet EH. Serum cystatin C, urinary neutrophil gelatinase-associated lipocalin and N-acetyl-beta-D-glucosaminidase in juvenile and adult patients with systemic lupus erythematosus: Correlation with clinical manifestations, disease activity and damage. Saudi J Kidney Dis Transpl. 2015 May-Jun;26(3):497-506. doi: 10.4103/1319-2442.157336.

Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Original Article

Effectiveness of Tolvaptan Treatment in Hyponatremic Patients

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Abstract

Introduction. Non-peptide vasopressin receptor antagonists (vaptans) are effective at increasing sodium in euvolemic and hypervolemic states and appear safe. We aimed to evaluate the efficacy of tolvaptan in euvolemic or hypervolemic hyponatremic patients.
Methods. The study included 9 hyponatremic (serum sodium level <125 mmol/L) patients. Serum potassium levels of all patients were normal and there was no acid-base disturbance. Patients with hypovolemic status and hepatic dysfunction were excluded from the study. Clinical and laboratory data of patients were obtained before and after tolvaptan treatment.
Results. The median age of patients (6 females, 3 males) was 66.63 years (range, 56-82). The mean sodium levels before tolvaptan treatment were 120.5 mEq/L (SD 2.2, range, 116-124). The mean sodium levels increased significantly to 132.6±4.0 mEq/L (range, 125-140) after tolvaptan treatment at 2.7±1.3 days (range, 2-6) ($p<0.001$). Hyponatremia did not recur after tolvaptan treatment. We did not observe serious adverse event related with tolvaptan treatment.
Conclusion. Hyponatremia was a common problem, and tolvaptan can treat hyponatremia effectively and safely in patients with euvolemic or hypervolemic hyponatremia.

Turk J Int Med 2020;2(2): 43-47
DOI: 10.46310/tjim.706226

Keywords: Arginine vasopressin, heart failure, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion, tolvaptan.

Introduction

Sodium (Na^+) is the major determinant of serum osmolarity and hyponatremia (Na^+ <135 mEq/L), being the most common electrolyte disorder in hospitalized patients with an incidence of 15-22%.[1] Patients with hyponatremia are asymptomatic or have mild symptoms, but in acute severe hyponatremia, serious neurological problems such as seizures, coma and respiratory

Received: March 19, 2020; Accepted: April 24, 2020; Published Online: April 29, 2020

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arrest may develop.[2] The two most common causes of hypervolemic and euvolemic hyponatremia are heart failure (HF) and syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH or Schwartz-Bartter syndrome), respectively.[3] In patients with HF, the effective circulation volume decreases due to the decrease in cardiac output, while the neurohumoral system, especially AVP and renin angiotensin aldosterone system are active.[4] Although the effective volume is normal in SIADH, ADH is released irregularly and uncontrolled or control mechanisms are disrupted due to tumors such as lung cancer, lung diseases, central nervous system diseases and some medications.[5] Serum Na^+ concentration is adjusted by arginine vasopressin (AVP, ADH), one of the pituitary hormones, by maintaining a balance between fluid intake and renal fluid excretion.[6] Under normal conditions, ADH is released in response to increased plasma osmolarity and decreased intravascular volume or decreased blood pressure. AVP has three different receptors. V1A receptor is associated with vasoconstriction and cardiac hypertrophy. V1B receptor is located in anterior pituitary gland, and associated with adrenocorticotropic hormone release. V2 receptor is located in the distal nephron, and increases free water reabsorption and water retention.[6,7]

Conventional approaches in the treatment of euvolemic or hypervolemic hyponatremia are fluid restriction and hypertonic saline infusion with diuretics. However, the effectiveness of fluid restriction is limited and patient compliance is poor. Besides, hypertonic saline infusion can correct sodium levels very quickly or diuretics can cause electrolyte disorders or acute kidney injury.[2] Vasopressin receptor antagonists bind to the V2 receptor and block the receptor, thereby increasing the concentration of serum Na^+ and diuresis. Tolvaptan, a vasopressin V2 receptor antagonist, selectively inhibits AVP binding to its receptor in the distal nephron and increases water excretion without disturbing the electrolyte balance. In recent years, tolvaptan has been used successfully in the treatment of hyponatremia in patients with heart failure, cirrhosis or SIADH.[8-10]

This study aimed to investigate the efficacy and safety of tolvaptan therapy on hyponatremia in patients with HF or SIADH.

Methods

A total of 9 euvolemic or hypervolemic hyponatremic (serum sodium level <125 mmol/L) patients with idiopathic SIADH or HF were included in this study conducted between July 2013 and September 2019. All patients with hypervolemic hyponatremic due to heart failure were initially treated with fluid restriction (1 L/day) and furosemide infusion and Na^+ replacement. Patients with heart failure did not have acute myocardial infarction, cardiogenic shock, valve disease or hypotension requiring inotropic support. The diagnosis of SIADH was made with euvolemic hyponatremia, hypoosmolality (serum osmolality <275 mOsm/kg), urine sodium level above 40 mEq/L and urine osmolality above 100 mOsm/kg. Kidney, liver, thyroid and adrenal function tests of SIADH patients with euvolemic hyponatremia were within normal ranges, and systolic ejection fractions were measured over 50% in echocardiographic evaluation. Serum potassium levels of all patients were normal, there was no acid-base disturbance. Patients with hypovolemic status and hepatic dysfunction were excluded from the study.

All patients were started with 15 mg/day tolvaptan treatment (Samsca 15 mg tablet, Abdi Ibrahim Otsuka) with fluid restriction (1 L/day). Diuretic therapy and/or Na^+ support was not performed simultaneously with tolvaptan. Serum Na^+ levels were checked 3 times on the first day of tolvaptan therapy and then daily. 24-hour diuresis was monitored and treatment was terminated when serum Na^+ was >133 mEq/L. Clinical and laboratory data of patients were obtained before and after treatment.

All statistical analyses were performed using the IBM SPSS Software package of version 23.0 (IBM Corp, Armonk, NY, USA). The data was given as mean±standard deviation (SD) or median (min-max). The numerical variables were compared with Wilcoxon signed-rank test within group. Statistical significance was defined by $p < 0.05$.

Results

A total of 9 patients (6 females, 3 males) were included. The mean patient age was 66.63 (range, 56 to 82) years Hyponatremia was due to previously diagnosed HF based on clinical and echocardiographic findings in 6 patients, whereas hyponatremia was related to SIADH in 3 patients.

Tolvaptan treatment was associated with significant increase in serum Na^+ values ($p<0.001$) and concomitant diuresis amount ($p=0.001$) (Figure 1) (Friedman's Two-Way Anova by ranks). None of the patients developed an increase in serum Na^+ concentration over 12 mEq/L within 48 hours of tolvaptan treatment. Xerostomia and thirst were the only side effects occurred under treatment with no records on other side effects such as confusion, muscle cramps, hypotension, hyperglycemia and liver enzyme elevation. No significant change was noted in serum creatinine levels after tolvaptan treatment ($p=0.522$) (Wilcoxon test). Dialysis or isolated ultrafiltration was not required in HF patients with low GFR. During the post-discharge 30-day follow up period, Na^+ levels maintained in the normal range with no need for re-hospitalization due to hyponatremia in any patient.

Discussion

Hyponatremia is an electrolyte disorders associated with re-hospitalization, prolonged length of hospital stay, increases risk of complications and cost increment. The efficacy of tolvaptan treatment in patients with hypervolemic hyponatremia was evaluated for the first time in a study by Gheorghiade et al. in 2003, while later studies and meta-analysis consistently reported the favorable efficacy of tolvaptan in the treatment of hypervolemic or euvolemic hyponatremia.[11,12] Tolvaptan treatment has been associated with increase in urinary output and serum Na^+ values along with reduction in hospitalization frequency and complications.[13-15] Similarly, our findings also revealed significant increase in serum Na^+ levels and daily diuresis with tolvaptan treatment.

In patients with HF, tolvaptan treatment protects renal functions in most of cases in contrast to diuretic treatment which has adverse effects on renal functions. In two different studies, tolvaptan treatment was reported to be associated with increased diuresis without disturbing renal functions and renal blood flow and without activating sympathetic nervous system and renin angiotensin aldosterone system.[9,10] Likewise, in the current study, tolvaptan treatment was not associated with renal dysfunction. In another study with 114 decompensated HF patients, authors reported significantly higher 24-hour and 48-hour urinary output and lower risk of poor renal parameters in the conventional plus tolvaptan treatment arm (n=44) as compared with conventional treatment arm (n=70).[16] Data from prospective randomized controlled Aquamarine study in 220 acute decompensated HF patients with GFR of 15-60 mL/min revealed superiority

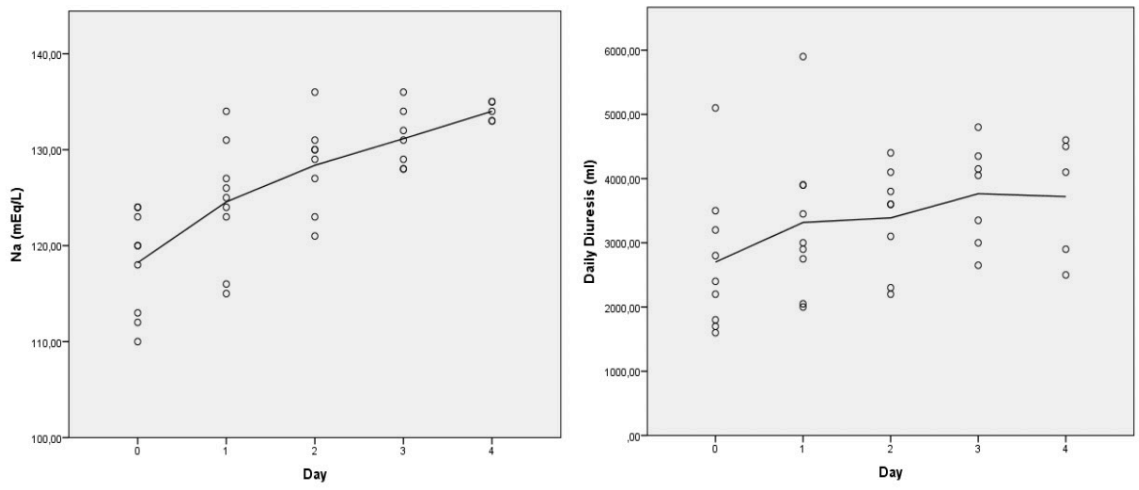

Figure 1. Serum Na values and urinary output under tolvaptan treatment

of tolvaptan over furosemide in terms of urinary output, serum Na^+ concentration and improvement of renal parameters.[17] In the current study no significant change was noted in renal functions after tolvaptan treatment in patients with low or normal GFR.

Data from SALT-1 and SALT-2 studies in patients with euvolemic or hypervolemic hyponatremia due to inappropriate ADH syndrome, HF or cirrhosis, tolvaptan versus placebo was reported to be associated with significantly higher 8-hour and 30-day serum Na^+ concentrations.[18,19] Our findings also revealed normal serum Na^+ levels within 30-day post-discharge follow up along with no need for re-hospitalization due to hyponatremia.

Our findings support the past studies indicated xerostomia and thirst as the most common tolvaptan-related side effects,[4,15,18,20] which were managed via symptomatic approach in our patients.

The major limitations of the current study seem to be the retrospective design, small sample size, lack of control group and a short follow up period.

Conclusions

In conclusion, while fluid restriction and loop diuretics with hypertonic fluid are treatment options with limited efficacy in euvolemic or hypervolemic hyponatremia, tolvaptan is a safe and effective treatment alternative. Tolvaptan seems to enable shorter length of hospital stay along with reductions in re-hospitalization frequency, dialysis requirement and hyponatremia-dependent morbidity and mortality rates. Further large scale studies are necessary to assess the long-term efficacy of tolvaptan on prognosis and renal parameters and to develop the optimal treatment protocol.

Acknowledgement

None to declare

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Verbalis JG. Hyponatremia: endocrinologic causes and consequences of therapy. Trends Endocrinol Metab. 1992 Jan-Feb;3(1):1-7.
2. Park GH, Lee CM, Song JW, Jung MC, Kim JK, Song YR, Kim HJ, Kim SG. Comparison of tolvaptan treatment between patients with the SIADH and congestive heart failure: a single-center experience. Korean J Intern Med. 2018 May;33(3):561-567. doi: 10.3904/kjim.2016.155.
3. Urso C, Brucculeri S, Caimi G. Employment of vasopressin receptor antagonists in management of hyponatraemia and volume overload in some clinical conditions. J Clin Pharm Ther. 2015 Aug;40(4):376-85. doi: 10.1111/ jcpt.12279.
4. Lilly LS, Dzau VJ, Williams GH, Rydstedt L, Hollenberg NK. Hyponatremia in congestive heart failure: implications for neurohumoral activation and responses to orthostasis. J Clin Endocrinol Metab. 1984 Nov;59(5):924- 30.
5. Gralla RJ, Ahmad F, Blais JD, Chiodo J 3rd, Zhou W, Glaser LA, Czerwiec FS. Tolvaptan use in cancer patients with hyponatremia due to the syndrome of inappropriate antidiuretic hormone: a posthoc analysis of the SALT-1 and SALT-2 trials. Cancer Med. 2017 Apr;6(4):723-729. doi: 10.1002/cam4.805.
6. Nemerovski C, Hutchinson DJ. Treatment of hypervolemic or euvolemic hyponatremia associated with heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone with tolvaptan: a clinical review. Clin Ther. 2010 Jun;32(6):1015-32. doi: 10.1016/j.clinthera.2010.06.015.
7. Nielsen S, Kwon TH, Christensen BM, Promeneur D, Frøkiaer J, Marples D. Physiology and pathophysiology of renal aquaporins. J Am Soc Nephrol. 1999 Mar;10(3):647-63.
8. Schrier RW, Sharma S, Shchekochikhin D. Hyponatraemia: more than just a marker of disease severity? Nat Rev Nephrol. 2013 Jan;9(1):37-50. doi: 10.1038/nrneph.2012.246.
9. Miyazaki T, Fujiki H, Yamamura Y, Nakamura S, Mori T. Tolvaptan, an orally active vasopressin V(2)-receptor antagonist - pharmacology and clinical trials. Cardiovasc Drug Rev. 2007 Spring;25(1):1-13.
10. Costello-Boerrigter LC, Smith WB, Boerrigter G, Ouyang J, Zimmer CA, Orlandi C, Burnett JC Jr. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. Am J Physiol Renal Physiol. 2006 Feb;290(2):F273-8.
11. Kinugawa K, Sato N, Inomata T. Effects of Tolvaptan on Volume Overload in Patients with Heart Failure. Int Heart J. 2018 Nov 28;59(6):1368-1377. doi: 10.1536/ ihj.18-119.
12. Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, Orlandi C; Tolvaptan Investigators. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation. 2003 Jun;107(21):2690-6.
13. Dasta JF, Sundar S, Chase S, Lingohr-Smith M, Lin J. Economic impact of tolvaptan treatment vs. fluid restriction based on real-world data among hospitalized patients with

heart failure and hyponatremia. Hosp Pract (1995). 2018 Oct;46(4):197-202. doi: 10.1080/21548331.2018.1505180.
14. Alskaf E, Tridente A, Al-Mohammad A. Tolvaptan for Heart Failure, Systematic Review and Meta Analysis of Trials. J Cardiovasc Pharmacol. 2016 Sep;68(3):196-203. doi: 10.1097/FJC.0000000000000405.
15. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA. 2007 Mar 28;297(12):1332-43.
16. Matsue Y, Suzuki M, Seya M, Iwatsuka R, Mizukami A, Nagahori W, Ohno M, Matsumura A, Hashimoto Y. Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure in high-risk population. J Cardiol. 2013 Feb;61(2):169-74. doi: 10.1016/j.jjcc.2012.08.020.
17. Matsue Y, Suzuki M, Nagahori W, Yoshida K, Onishi Y, Satoh Y, Ono Y, Nishioka T, Noda M, Sugi K, Torii S, Tejima T, Sakurada H, Yamaguchi S, Okishige K, Fujii H, Takahashi A. Clinical effectiveness of tolvaptan in patients with acute decompensated heart failure and renal failure: design and rationale of the AQUAMARINE study. Cardiovasc Drugs Ther. 2014 Feb;28(1):73-7. doi: 10.1007/s10557-013-6491-8.
18. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006 Nov 16;355(20):2099-112.
19. Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS; SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol. 2011 May;164(5):725-32. doi: 10.1530/ EJE-10-1078.
20. Gheorghiade M, Gottlieb SS, Udelson JE, Konstam MA, Czerwiec F, Ouyang J, Orlandi C; Tolvaptan Investigators. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. Am J Cardiol. 2006 Apr 1;97(7):1064-7.

Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
CASE REPORT

Herpes zoster ophthalmicus infection after kidney transplantation

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Abstract

Herpes zoster causes an acute dermatomal infection with vesicular rash associated with reactivation of the Varicella zoster virus. The infection usually involves the thoracic, cervical, ophthalmic and lumbosacral regions. Herpes zoster infection is common after solid organ transplantation. Herpes zoster ophthalmicus is a rare form of Herpes zoster infection and involves the ophthalmic branch of the trigeminal nerve along the V1-V2 dermatomes. Herein, we reported a kidney recipient who developed Herpes zoster ophthalmicus infection after transplantation.

Keywords: Herpes zoster, infection, kidney transplantation, ophthalmic involvement.

Turk J Int Med 2020;2(2):48-50
DOI: 10.46310/tjim.691092

Introduction

The infections after kidney transplantation are associated with significant morbidity and mortality. Herpes zoster (shingles) is caused by the reactivation of latent Varicella zoster virus (VZV), which gained access to sensory ganglia during varicella. Adult recipients are at high risk for the development of VZV-related disease (chickenpox and herpes zoster) after kidney transplantation due to long-term immunosuppression.[1] VZV reactivation is increased in the elderly and immunocompromised individuals. It can cause an acute dermatomal infection, often accompanied by a vesicular rash that involves the thoracic, cervical, ophthalmic and lumbosacral regions.[2] Herpes zoster ophthalmicus is defined as herpes zoster involvement of the ophthalmic branch of the fifth cranial (trigeminal) nerve along the V1-V2 dermatomes. It is characterized by painful unilateral vesicular eruption in different stages, and usually occurs in a restricted dermatomal distribution. We presented a kidney recipient who developed Herpes zoster ophthalmicus after transplantation.

Received: February 19, 2020; Accepted: April 25, 2020; Published Online: April 29, 2020

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Case Report

A 48-year-old female patient underwent kidney transplantation 7 years ago due to end-stage kidney disease of unknown cause. Maintenance immunosuppressive therapy consisted of prednisolone, tacrolimus and mycophenolate mofetil (MMF). The patient was admitted to the emergency room with complaints of weakness, myalgia, headache and a yellow-dried vesicular rash extending to the forehead, nose, right eyelid and the scalp for the last 5 days (Figure 1a). In her laboratory tests; leukocyte was 7240 cell/mm^3, hemoglobin 13.8 g/dL, platelet 230,000 cell/mm^3, creatinine 2.7 mg/dL, AST 70 IU/L and ALT 132 IU/L. With the diagnosis of herpes zoster ophthalmicus and peri-orbital cellulitis 750 mg acyclovir, 4 g ceftriaxone, 1200 mg linezolid and 1000 mg metranozidol treatments were started daily. Her endoscopic examination revealed no lesions compatible with rhinocerebral mucormycosis. On eye examination, keratitis was detected. Paranasal CT and orbital MR were compatible with pre-septal cellulitis. Wet spunch dressing treatments were added with local valgancyclovir, ciprofloxacin and saline. AST (21 IU/L) and ALT (58 IU/L) regressed on the 5th day of parenteral treatment. Fever was not observed, headache complaint subsided, and edema around the eyelid completely disappeared. Some of the lesions were dried and some were completely disappeared (Figure 1b). The patient was discharged after 14 days of medical treatment.

Discussion

Herpes zoster ophthalmicus is a potentially sight-threatening condition. Its incidence rates varies from 8% to 20%.[3-5] The prodromal period begins with headaches, malaise and fever. Unilateral pain or hypesthesia can be seen above the affected eye, forehead and top of head. Hyperemic conjunctivitis, uveitis, episcleritis and keratitis may occur at the onset of the rash.[6] In our case with herpes zoster ophthalmicus due to cranial nerve involvement, keratitis was present. In VZV infections, the diagnosis is made by the presence of vesicles that form groups on erythematous ground in the skin region that characteristically correspond to the sensory nerve dermatome. In our patient, there were vesicular eruptions of the ophthalmic branch of the trigeminal nerve (V1) that formed groups in the area suitable for the dermatome area of the sensory nerve. Herpes simplex virus (HSV) infections, which may occasionally be typical shingles-like rashes, should also be considered in the differential diagnosis. Thoracolumbar region involvement is more common in Herpes zoster cases.[7] Herpes IgM should be negative in VZV infection. In our patient, both herpes IgG and IgM were negative.

Reactivation is thought to be associated with suppression of cellular immunity. Herpes zoster keratitis and ophthalmicus are serious complications after cranial herpes infection.[8] The incidence of Herpes zoster ophthalmicus in hospitalized immunosuppressive patients increases up to 35%. Malignancy, radiotherapy or chemotherapy, organ transplantation and long-term corticosteroid use

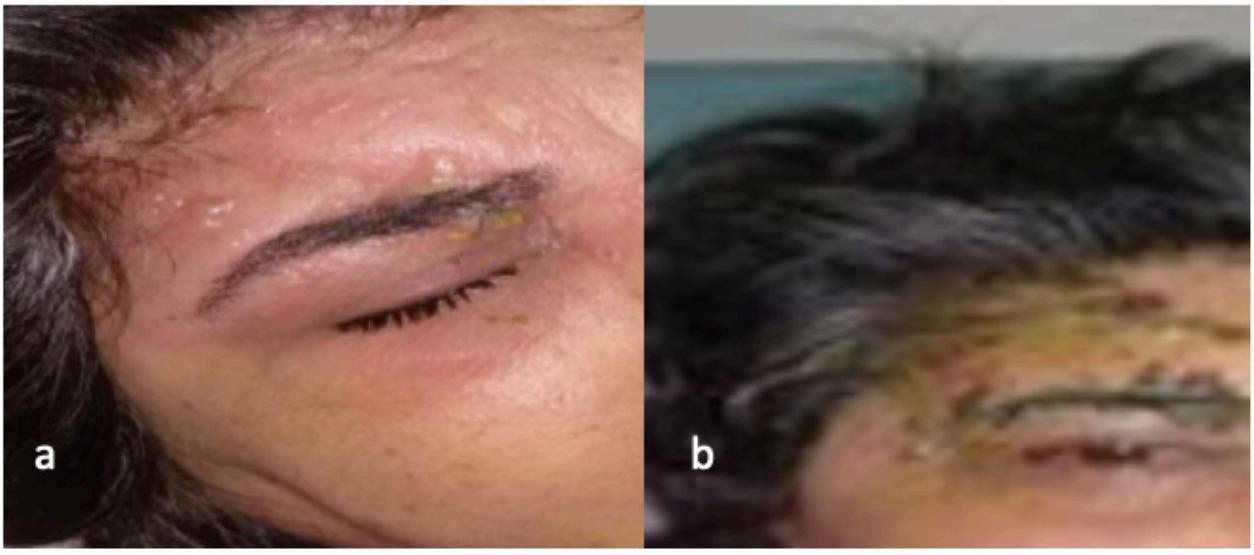

Figure 1. The appearrence of her eye involvement before (a) and after (b) the treatment

are risk factors. Risk factors for the development of Herpes zoster in kidney transplant recipients are >50 years of age, long-term induction therapy and CMV prophylaxis.[9] In some studies, MMF has been reported as a risk factor for Herpes zoster in kidney transplant recipients. Complications such as scar, encephalitis, hepatitis, disseminated intravascular coagulation and pneumonia may be observed after Herpes zoster infection.[10] Our patient had hepatitis. Herpetic post-neuralgia (PNH) is a complication characterized by persistent pain that develops after acute pain and negatively affects quality of life and daily activities. Advanced age and the presence of immunosuppression are reported as factors associated with the development of PNH.[11] Our patient did not develop PHN. Screening for VZV in adults and immunization to susceptible individuals before transplantation is recommended for the prevention of primary VZV infection in adult patients scheduled for kidney transplantation.[12] Chickenpox vaccine can prevent the reactivation of the virus by increasing cellular immunity against the virus. Because VZV specific memory T-cell number decreases with age. When this decrease falls below the threshold, the risk of Herpes zoster development increases. Therefore, vaccine application can prevent Herpes zoster development by keeping VZV-specific T-cell formation above the threshold value.[13] Complications such as primary varicella infection, recurrent zoster infections and pneumonia in immunocompromised patients are treated parenteral acyclovir (every 8 hours, 10 mg/kg).

Ocular manifestations of Herpes zoster include lids, cornea, conjunctivae, uvea and retina involvements. The diagnosis of Herpes zoster may be difficult in immunosuppressed patients and should be considered in the differential diagnosis of acute headache in kidney transplant recipients.[14] Occult infection is always possible, sometimes symptoms, signs, and routine tests can be misleading. Vesicular lesions on the side or tip of the nose are highly associated with eye involvement. Lesions in this area of the face indicate the involvement of the nasociliary branch of the trigeminal nerve.[6] Therefore, early diagnosis and treatment of Herpes zoster infection after kidney transplantation is important to prevent progressive corneal involvement and potential vision loss.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Chen SY, Suaya JA, Li Q, Galindo CM, Misurski D, Burstin S, Levin MJ. Incidence of herpes zoster in patients with altered immune function. Infection. 2014 Apr;42(2):325-34. doi: 10.1007/s15010-013-0550-8.
2. Arness T, Pedersen R, Dierkhising R, Kremers W, Patel R. Varicella zoster virus-associated disease in adult kidney transplant recipients: incidence and risk-factor analysis. Transpl Infect Dis. 2008 Jul;10(4):260-8.
3. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. Ophthalmology. 2008 Feb;115(2 Suppl):S3-12. doi: 10.1016/j.ophtha.2007.10.009.
4. Pavan-Langston D. Herpes zoster ophthalmicus. Neurology. 1995 Dec;45(12 Suppl 8):S50-1.
5. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore). 1982 Sep;61(5):310-6.
6. Mary A Albrecht MA, Levin MJ. Epidemiology, clinical manifestations, and diagnosis of herpes zoster. In: Hirsch MS, Mitty J, editors. UpToDate [Internet]. Waltham (MA): UpToDate Inc; 2020 [cited 2020 Feb]. Available from: https://www.uptodate.com/contents/ epidemiology-clinical-manifestations-and-diagnosis-of-herpes.
7. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007 Nov;82(11):1341-9.
8. Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. Arch Intern Med. 1997 Jun 9;157(11):1209-13.
9. Gourishankar S, McDermid JC, Jhangri GS, Preiksaitis JK. Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era. Am J Transplant. 2004 Jan;4(1):108-15.
10. Lauzurica R, Bayés B, Frías C, Fontseré N, Hernandez A, Matas L, Jimenez A, Bonet J, Romero R. Disseminated varicella infection in adult renal allograft recipients: role of mycophenolate mofetil. Transplant Proc. 2003 Aug;35(5):1758-9.
11. Hong MJ, Kim YD, Cheong YK, Park SJ, Choi SW, Hong HJ. Epidemiology of Postherpetic Neuralgia in Korea: An Electronic Population Health Insurance System Based Study. Medicine (Baltimore). 2016 Apr;95(14):e3304. doi: 10.1097/MD.0000000000003304.
12. Hata A, Asanuma H, Rinki M, Sharp M, Wong RM, Blume K, Arvin AM. Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. N Engl J Med. 2002 Jul 4;347(1):26-34.
13. Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. N Engl J Med. 2007 Mar 29;356(13):1338-43.
14. Ostermann ME, Gyawali P, Snowden SA, Eastwood JB, Streather CP. A 67-year-old kidney transplant patient with headache of uncertain origin. Nephrol Dial Transplant. 2002 Mar;17(3):508-10.

Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
CASE REPORT

A Case of Pituitary Insufficiency in a Patient Presenting with Hyponatremia: Might Be Slow-Progressing Lymphocytic Hypophysitis as a Possible Cause of Empty Sella?

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Abstract

Pituitary insufficiency is a clinical condition arising from the deficiency of one or more of the pituitary hormones. Hypophysitis generally involves lymphocytic, granulomatous, plasmacytic and xantomatous infiltration and its diagnosis requires histological confirmation. The most common cause of hypophysitis is "lymphocytic hypophysitis".

A 75-year-old female patient presented with complaints of nausea, weakness, fatigue and generalized pain all over her body. Her medical history included essential hypertension, type 2 Diabetes Mellitus, coronary artery disease and hypothyroidism. She was hospitalized due to detecting a serum sodium (Na) concentration of 123 mmol/L. Although her diuretic medications were discontinued and fluid replacement with parenteral hypertonic saline infusion was instituted for approximately 6 days, Na level did not return to normal. Secondary hypothyroidism was considered due to laboratory test results showing low fT_4 level and markedly suppressed TSH value. Since further laboratory workup showed that TSH, ACTH, PRL, GH and gonadotropins were also low, the diagnosis was confirmed as "panhypopituitarism". Her obstetric history was not suggestive of Sheehan's Syndrome and she did not have a history of head injury or cerebrovascular disease. She was started on parenteral 100 mg hydrocortisone and hormonal replacement therapy with oral levothyroxine. The clinical picture of the patient improved dramatically with resolution of hyponatremia.

Lymphocytic hypophysitis is an autoimmune disorder of the pituitary gland and it mostly affects middle-aged women. The fact that our patient was the age of 75 without having any clinical symptoms, since she had "panhypopituitarism" and a "partially empty sella" appearance in her pituitary MRI scans, "lymphocytic hypophysitis" was considered as the probably cause of pituitary insufficiency even if her age was older than the typical age of patients affected by the condition. It suggests that slow-progressing primary hypophysitis (probably lymphocytic hypophysitis) can lead to pituitary insufficiency at a later age.

Turk J Int Med 2020;2(2):51-55
DOI: 10.46310/tjim.714043

Keywords: *Hyponatremia, pituitary insufficiency, lymphocytic hypophysitis.*

Received: April 06, 2020; Accepted: April 26, 2020; Published Online: April 29, 2020

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Introduction

Hyponatremia, defined as a serum sodium (Na^+) concentration less than 135 mmol/L, is the most common type of electrolyte disturbance. The biochemical finding of a serum sodium concentration between 130-135 mmol/L as measured by an ion specific electrode is classified as "mild" hyponatremia, a serum sodium concentration between 125-129 mmol/L as "moderate" hyponatremia and a serum sodium concentration less than 125 mmol/L as "profound" hyponatremia". Severe hyponatremia is a potentially life-threatening condition and a significant cause of morbidity and mortality. Mild-to-moderate hyponatremia (a Na^+ value ranging from 125 to 135 mmol/L) is known to have a significant effect on cognitive function, particularly in older patients. Hyponatremia can also be classified based on time of development and 'acute' hyponatremia is defined as hyponatremia that is documented to exist < 48 hours and 'chronic' hyponatremia as hyponatremia that is documented to exist for at least 48 hours. It is crucial to determine whether hyponatremia has developed acutely or had been present on a chronic basis and identify the underlying etiology of hyponatremia in order to provide corrective therapy. It is equally important to establish whether the patient is "hypovolemic", "hypervolemic" or "euvolemic" on the basis of physical examination findings.[1,2]

Euvolemic hyponatremia can develop as a result of glucocorticoid deficiency, the syndrome of inappropriate antidiuresis(SIAD), hypothyroidism, stress and medications and the urinary Na^+ level is greater than 20 mmol/L.[1-3] Other causes should be excluded in order to make a diagnosis of SIAD.[3,4] Glucocorticoid deficiency can be caused by primary or secondary adrenal insufficiency. Secondary adrenal insufficiency occurs when the adrenal cortex fails to produce adequate amounts of glucocorticoids as a result of insufficient adrenocorticotropic hormone (ACTH) secretion from the pituitary gland. ACTH deficiency may occur alone or in combination with deficiencies of other pituitary hormones.[5] Hypothalamic hormone deficiencies may also cause pituitary insufficiency due to absent stimulation of pituitary hormone secretion. Pituitary insufficiency is a clinical condition arising from the deficiency of one or more of the pituitary hormones. Pituitary hormone deficiency is associated with several morbidities that affect patient quality of life adversely and can even cause mortality. Many conditions can lead to pituitary insufficiency. Primary pituitary deficiency, traumatic brain injury, pituitary adenomas, pituitary surgery, infiltrative disorders that involve the pituitary gland or other organ tumors metastasizing to the pituitary gland may cause hypopituitarism.[6] Another cause of primary pituitary insufficiency is "hypophysitis" which is the inflammation of the pituitary gland that occurs due to various reasons. Hypophysitis generally involves lymphocytic, granulomatous, plasmacytic and xantomatous infiltration and its diagnosis requires histological confirmation. The most common cause of hypophysitis is "lymphocytic hypophysitis". Patients with lymphocytic hypophysitis test positive for antipituitary antibodies. The gold standard method for the diagnosis of lymphocytic hypophysitis involves identification of the histopathology by "pituitary gland biopsy". However, the diagnosis usually is established by clinical findings and demonstration of pituitary hormone deficiencies. The diagnosis is supported when there is a deficiency of one or more of the pituitary hormones.[6,7] Pituitary MRI scan shows a partially or completely empty Sella during the later stages of lymphocytichypophysitis.[8-10]

Case Report

A 75-year-old female patient presented to the emergency room with complaints of nausea, weakness, fatigue and generalized pain all over her body. Her medical history included essential hypertension, type 2 diabetes mellitus (DM), coronary artery disease and hypothyroidism and was being followed at the Internal Medicine outpatient clinic of our hospital. Her current treatment included a combination of irbesartan and hydrochlorothiazide, indapamide, metformin, gliclazide, isosorbide monohydrate, acetyl salicylic acid and levothyroxine.

Medical History: The patient had hypertension for about 20 years and type 2 DM for 15 years. Her current treatment included a combination of irbesartan and hydrochlorothiazide, indapamide, metformin, gliclazide, isosorbide monohydrate and acetyl salicylic acid. She has been receiving levothyroxine at a dose of 100 mcg/day since a thyroid surgery that she underwent almost 25 years ago. A TSH test was requested by the Internal Medicine outpatient clinic about 6 months ago which showed TSH suppression (possibly due to secondary hypothyroidism), resulting in lowering of the levothyroxine dose to 75 mcg/day.

The patient had a daughter who was 52 years old at the time of her presentation and she did not report

any problems during her pregnancy or complications at childbirth. She had breastfed her daughter. She had regular menses after the delivery and entered menopause at 50 years of age. She did not report a history of a trauma to the head or cerebrovascular disease.

Physical Examination: Her general condition was moderate, and she was in a confused state. Her arterial blood pressure was 100/60 mmHg and heart rate was 99 beats per minute. There were no findings of marked dehydration or hypervolemia.

Clinical Course: The patient was admitted to the Internal Medicine department upon detecting a serum sodium (Na^+) concentration of 123 mmol/L obtained at the emergency room. Her diuretic medications were discontinued, and parenteral saline infusion was initiated. Serum Na^+ levels measured at about 6 months and 1 year prior to her admission were in normal limits as documented in her previous laboratory data stored in our hospital's archives (Table 1).

Table1. Laboratory values of the patient

Parameters	At 1 year prior to admission	At 6 months prior to admission	On admission	Before starting steroids	1 day after starting steroids	On final follow-up
Hb (g/dL)	12.2	11.68	12.22	11.41	12.21	12.28
Hct (%)	38.7	35.1	35.3	34.6	36.6	37.6
WBC (uL)	6300	7480	4670	5170	8780	7300
Platelet (10^3/uL)	197	229	288	298	335	221
MCV (FL)	93	92	94	92	93	93
Glucose (mg/dL)	128	125	225	102	264	181
Urea (mg/dL)	43	37	20	23	22	51
Creatinine (mg/dL)	0.86	0.82	0.65	0.81	0.83	0.93
Na (mmol/L)	138	141	125	124	130	141
K (mmol/L)	4.83	5.07	4.1	4.38	5.0	4.64
Cl (mmol/L)	-	-	88.8	94.9	98.2	-
Ca (mg/dL)	-	-	8.9	8.3	8.9	-
P (mg/dL)	-	-	3.6	2.9	2.5	-
AST (IU/L)	15	16	22	23	33	11
ALT (IU/L)	13	12	17	11	12	11

Hb= hemoglobin, Hct= hematocrit, WBC= white blood cells, MCV= mean corpuscular volume, Na= Sodium, K= Potassium, Ca= Calcium, P= Phosphorus, AST= Aspartate aminotransferase, ALT= alanine aminotransferase

Table 2. Hormone values of the patient

Parameters	At 1 year prior to admission	At 6 months prior to admission	On admission	On final follow-up
fT3 (pg/ml)	-	.	1.82	-
fT4 (ng/dL)	1.39	1.50	0.916	1.09
TSH (mIU/L)	0.215	0.369	<0,005	-
Anti-TPO (IU/mL)	-	-	21.69	-
Anti-TG (IU/mL)	-	-	24.42	-
Cortisol (ug/dL)	-	-	1.76	-
ACTH (pg/ml)	-	-	3.15	-
FSH (mIU/mL)	-	-	7.5	-
LH (mIU/mL)	-	-	2.75	-
E2 (pg/mL)	-	-	5	-
PRL (ng/mL)	-	-	8.3	-
IGF-1 (ng/mL)	-	-	39.6	-

fT3= free T3, fT4= free T4, TSH= Thyroid stimulating hormone, Anti-TPO= Anti-thyroid peroxidase, Anti-TG= Anti-thyroglobuline, ACTH= adrenocorticothyropine hormone, FSH= Follicle stimulating hormone, LH= Luteinizing hormone, E2= estradiole, PRL= prolactine, IGF-1= insulin like growth factor-1

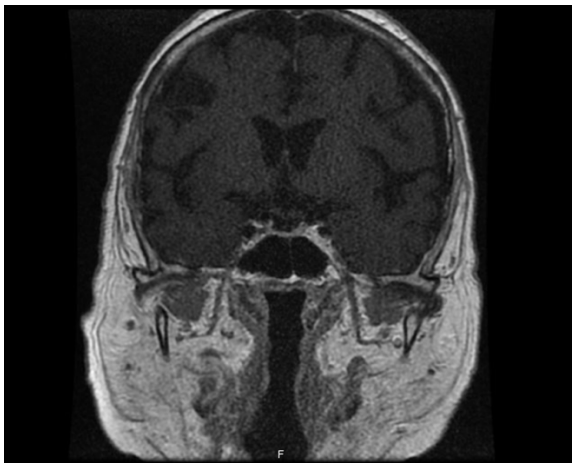

Figure 1a. Coronal section of the pituitary gland on pituitary MRI scan.

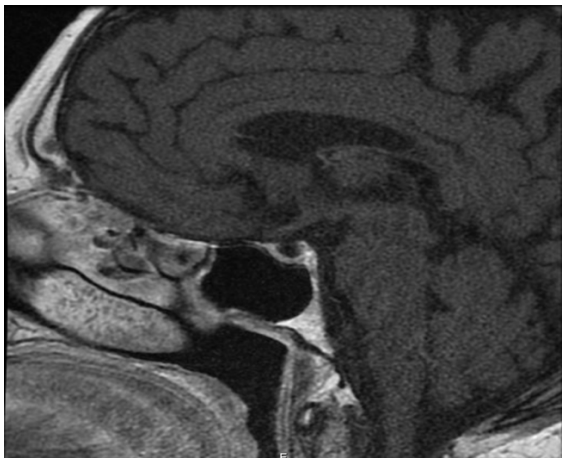

Figure 1b. Sagittal section of the pituitary gland on pituitary MRI scan.

A TSH test requested by the Internal Medicine outpatient clinic about 6 months ago showed suppressed TSH, resulting in lowering of the levothyroxine dose to 75 mcg/day from 100 mcg/day (Table 2).

No other laboratory tests were performed after her follow-up 6 months ago until her presentation to the emergency room with hyponatremia.

Although the patient's diuretic medications were discontinued and fluid replacement with parenteral hypertonic saline infusion was instituted for approximately 6 days, Na level did not return to normal and thus, the patient was evaluated for the underlying reasons of hyponatremia. Secondary hypothyroidism was considered due to laboratory test results showing low fT4 level and markedly suppressed TSH value, which led to measurement of baseline plasma cortisol (BC) level to investigate secondary adrenal insufficiency. Subsequently, the patient was diagnosed with pituitary insufficiency based on a BC level of 1.75 µg/dL. Since TSH, ACTH, PRL, GH and gonadotropins were also low, the diagnosis was confirmed as "panhypopituitarism". The images obtained with a pituitary MRI scan were consistent with "empty Sella" (Figures 1a and 1b).

Testing for anti-pituitary antibodies could not be obtained as this is not routinely performed at our hospital laboratory. The images from a pituitary MRI scan were consistent with "empty Sella" appearance. Initially, the patient was started on parenteral 100 mg hydrocortisone and hormonal replacement therapy with oral levothyroxine. The clinical picture of the patient improved dramatically with resolution of hyponatremia. She was discharged on oral hydrocortisone and levothyroxine replacement.

Discussion

As suggested by the medical history of the patient, she had manifestations of slow progressing panhypopituitarism which led to her presentation to the emergency room with symptoms of hyponatremia. "Pituitary insufficiency" was suspected due to refractory hyponatremia and persistently low TSH values suggestive of secondary hypothyroidism during her hospitalization at the ICU, leading to a final diagnosis of pituitary insufficiency. In this patient, cortisol deficiency due to ACTH insufficiency was treated with steroid replacement and her clinical symptoms and hyponatremia improved dramatically post-treatment. Since our patient did not have a history of traumatic brain injury, pituitary adenomas, pituitary surgery, infiltrative disorders that involve the pituitary gland, other organ tumors metastasizing to the pituitary gland or Sheehan's syndrome that could explain pituitary insufficiency, "primary hypophysitis" was considered as the cause of pituitary insufficiency.[6,7] "Lymphocytic hypophysitis" has been reported as a cause of primary hypophysitis that results in chronic and slow-progressing pituitary insufficiency. Lymphocytic hypophysitis is an autoimmune disorder of the pituitary gland and it mostly affects middle-aged women. Over time, pituitary insufficiency ensues due to lymphocytic hypophysitis and appearance of partially or completely empty Sella can be demonstrated by pituitary MRI scans.[8-11] However, manifestations of "panhypopituitarism" were evident in our patient at an advanced age. Since she had "panhypopituitarism" and a "partially empty Sella" appearance in her pituitary MRI scans, "primary hypophysitis (probably lymphocytic hypophysitis)"

was considered as the cause of pituitary insufficiency even if her age was older than the typical age of patients affected by the condition. The fact that our patient could reach the age of 75 without having any clinical symptoms of the disease suggests that primary hypophysitis (probably lymphocytic hypophysitis) can lead to pituitary insufficiency at a later age with a slow progressive course.

As patients with secondary hypothyroidism have a decreased secretion of TSH because of pituitary insufficiency, the dosage should be adjusted taking into account the fT_4 level during levothyroxine replacement therapy. Growth hormone replacement therapy was not given to our patient since she was at an advanced age and her clinical condition improved considerably with the treatments provided. The patient was discharged with routine clinical follow-up care.

Conclusion

Lymphocytic hypophysitis mostly affects middle-aged women. However, manifestations of "panhypopituitarism" were evident in our patient at an older age. It suggests that slow-progressing primary hypophysitis (probably lymphocytic hypophysitis) can lead to pituitary insufficiency at a later age.

Acknowledgements:

This case was partly reported as a poster presentation at 41st Congress of Endocrinology and Metabolism held between April, 27 - May 1, 2019, Antalya, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Sterns RH. Disorders of plasmasodium-causes, consequences, and correction. N Engl J Med . 2015 Jan 1;372(1):55-65. doi: 10.1056/NEJMra1404489.
2. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E; Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant. 2014 Apr;29 Suppl 2:i1-i39. doi: 10.1093/ndt/ gfu040.
3. Grant P, Ayuk J, Bouloux PM, Cohen M, Cranston I, Murray RD, Rees A, Thatcher N, Grossman A. The diagnosis and management of inpatient hyponatraemia and SIADH. Eur J Clin Invest. 2015 Aug;45(8):888-94. doi: 10.1111/eci.12465.
4. Cuesta M, Thompson CJ. The syndrome of inappropriate antidiuresis (SIAD). Best Pract Res Clin Endocrinol Metab. 2016 Mar;30(2):175-87. doi: 10.1016/j.beem.2016.02.009.
5. Garrahy A, Thompson CJ. Hyponatremia and Glucocorticoid Deficiency. Front Horm Res. 2019;52:80-92. doi: 10.1159/000493239.
6. Gubbi S, Hannah-Shmouni F, Stratakis CA, Koch CA. Primary hypophysitis and other autoimmune disorders of the sellar and suprasellar regions. Rev Endocr Metab Disord. 2018 Dec;19(4):335-47. doi: 10.1007/ s11154-018-9480-1.
7. Korkmaz OP, Sahin S, Ozkaya HM, Apaydin T, Durmaz ES, Haliloglu O, Durcan E, Kadioglu P. Primary hypophysitis: Experience of a Single Tertiary Center. Exp Clin Endocrinol Diabetes. 2019 Jun 24. doi: 10.1055/ a-0919-4388. [Epub ahead of print].
8. Gao H, Gu YY, Qiu MC. Autoimmune hypophysitis may eventually become empty sella. Neuro Endocrinol Lett. 2013;34(2):102-6.
9. Nishiyama S, Takano T, Hidaka Y, Takada K, Iwatani Y, Amino N. A case of postpartum hypopituitarism associated with empty sella: possible relation to postpartum autoimmune hypophysitis. Endocr J. 1993 Aug;40(4):431-8.
10. Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F, Donmez H. Empty sella may be the final outcome in lymphocytic hypophysitis. Endocr Res. 2009;34(1-2):10-7. doi: 10.1080/07435800902841306.
11. Ishikawa S, Furuse M, Saito T, Okada K, Kuzuya T. Empty sella in control subjects and patients with hypopituitarism. Endocrinol Jpn. 1988 Oct;35(5):665-74.

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