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ORIGINAL RESEARCH GERIATRIC ANESTHESIA

Hyponatremia in elderly patients with fractures around the hip; role of glutamate (CSF glutamate study)

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Abstract

Background & objective: Hyponatremia is the most common electrolyte disorder and is a predictor of osteoporosis, inflammation and cognitive dysfunction leading to falls in the elderly patients. We compared glutamate levels in normonatremic elderly patients with those with hyponatremia, admitted with osteoarthritis, to find correlation between the cognitive status with cerebrospinal fluid (CSF) glutamate as a biomarker for hyponatremia.

Methodology: In an observational prospective study; 70 patients, more than 70 y of age, admitted to trauma unit of Assiut University Hospital with fractures around the hip, were investigated for the frequency of on-admission hyponatremia. The CSF glutamate level was determined using radio-immune assay. We compared glutamate level in 18 hyponatremic patients with 10 normonatremic elderly patients admitted with osteoarthritis for elective joint replacement (control group) to find correlation between the cognitive status assessed by Modified Mini-Mental State (3MS) examination and CSF glutamate as a biomarker for hyponatremia.

Results: Hyponatremia is highly prevalent in elderly with fractures around the hip; we recorded it in 41.4% of the study sample. Most patients were females (62.86%). CSF glutamate was significantly increased in hyponatremic patients than the controls ($P < 0.001$).

Conclusion: Prevalence of hyponatremia is high in old aged patients probably due to due to prevalent hot weather in the south of Egypt. CSF glutamate level can be a marker for mild cognitive impairment caused by hyponatremia.

Abbreviations: 3MS: Modified Mini-Mental State examination; CSF: cerebrospinal fluid; RPM: revolutions per minute; ELISA: enzyme-linked immunosorbent assay; SD: standard deviation

Key words: Geriatric anesthesia; Chronic Disease; Cognition Disorders / blood; Cognition Disorders / etiology; Glutamic Acid / metabolism; Hyponatremia / blood; Hyponatremia / complications; Hyponatremia / psychology; Inappropriate ADH Syndrome / complications; 3MS

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1. Introduction

Sodium is a precise element in human body, and there is a close relationship between sodium and the brain function. The most common electrolyte disorder is hyponatremia; and is mostly known for its neurological problems. Unrecognized complications of hyponatremia include falls, osteoporosis and fractures. Gait disturbance, cognitive dysfunction, and falls can occur with hyponatremia just below 135 meq/L. [1, 2] Fractures around the hip in elderly is a global problem. Every year, around 1.6 million patients suffer from hip fractures worldwide. As the population grows, there is an increase of this incidence by 25% by every decade. [3]

Unfortunately, hip fracture and its repair have higher mortality rate than elective hip replacement by 6 to 15 folds. The explanation for this may be due to higher incidence of preexisting medical diseases in the fracture patients; 75% of them are over 70 y and 95% present with at least one major preoperative comorbidity. [3, 4]

Hyponatremia is not uncommon in geriatric patients, and it may be accompanied by hypothyroidism, hypocortisolism, congestive heart failure, and renal or hepatic dysfunction. Multidrug administration is another challenge in such patients e.g. antihypertensives, antiepileptics, and antidepressants along with homeostatic stress occurred with the onset of fracture itself and its subsequent surgery. [5] Geriatric patients with even mild hyponatremia commonly experience increased rates of fractures and falls. Falls are serious health problem for the elderly and account for about 50 percent of deaths due to injury in the elderly. In fact, age is a nonmodifiable risk factor, but falls are preventable. [5, 6]

The primary objective was to detect the frequency of hyponatremia in elderly patients with fractures around the hip. Secondary goals included the effect of hyponatremia on mental status of the patients by using Modified Mini-Mental State (3MS) examination, [7] and the mortality rate for 6 months post admission. We also evaluated the cerebrospinal fluid (CSF) glutamate levels to compare it in hyponatremic with normonatremic patients, to find any correlation between the cognitive status.

2. Methodology

It was a prospective observational study, carried out in our university hospital. Patients' enrollment started after obtaining approval of hospital ethical committee; and registration in the clinical trials under number (NCT03456492).

Part one

Inclusion criteria included patients aged 70 y or more with fracture around the hip, who could communicate and reply to questions for assessment of mental status through 3MS examination who were admitted to our hospital trauma unit over one year. On admission, informed consent was taken from the participants or their guardians. Full medical history was taken followed by clinical examination of the volume status. Assessment of the mental status of the patients was done by 3MS examination (screening test for dementia). Cognitive impairment was identified as a 3MS score < 80. [8] Serum sodium level was screened as a part of basic preoperative laboratory work up.

Part two

Eighteen hyponatremic elderly patients with mild hyponatremia from those who were included in part one (case group) compared with 10 normonatremic elderly patients admitted with osteoarthritis for elective joint replacement (control group). Cerebrospinal fluid glutamate level was detected as follows; CSF samples were collected during spinal anesthesia procedure, centrifuged at 2000-3000 revolutions per min (RPM), and kept at −20 °C till the time of the assay. CSF were analyzed for glutamate by enzyme-linked immunosorbent assay (ELISA) kit, Catalog number (BYEK3195-8) supplied by Chongqing Biopsies Co., Ltd in China (www.biospes.com) according to the manufacturer's instructions.

Statistical analysis

Data were collected and checked for normality of distribution through Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation or error, number (percentage), or median (range) as appropriate. Statistical significance between groups was determined by using independent t-test and Mann-Whitney test for matching distributed data. Statistical significance was considered when $P \leq 0.05$. Data were investigated employing the computer program IBM, SPSS (Statistical Package for Social Sciences), Version 22, 2015.

3. Results

The demographic data of the main study group (n = 70) demonstrates that the participants were mostly females with a ratio of 2:1. Signs of dehydration as sunken eyes, dry cracked tongue, decreased skin turgor, tachycardia and hypotension were detected in 70% of patients. The incidence of femur-neck fractures was highest among all types of fractures around the hip. Fractures most commonly resulted from falling on the ground (Table 1).

Hyponatremia was prevalent in 41.4% of the patients, and the degree was mild (130-135 mmol/L) in majority of them. Seventeen patients died within 6 months post

Table 1: Demographic and clinical data of the case group

Parameter		Study group (n = 70)
Age (y)		76.5 ± 5.6
Gender	- Male	26 (37.14)
	- Female	44 (62.86)
Education level	- Illiterate:	65 (93)
	- Primary level:	3 (4.2)
	- Secondary level	2 (2.8)
Comorbidities	- Hypertension	21 (29.5)
	- Diabetes	16 (22.5)
Fracture type	- Fracture neck of femur	42 (60)
	- Trochanteric fracture	22 (31.4)
	- Intertrochanteric fracture	1 (1.4)
	- Subtrochanteric fracture	3 (4.3)
	- Acetabular fracture	2 (2.9)
	- Fracture caused by falling	65 (92.9)

Data are presented as mean ± standard deviation or number (percentage)

Table 2: Clinical, laboratory data, and outcome of the case group

Variable	Study group (n = 70)
Dehydrated patients	49 (70)
Hyponatremia	29 (41.4)
- Mild degree (135-130 mmol/L)	26 (37.1)
- Moderate degree (129-125 mmol/L)	3 (4.3)
3MS score	49.3 ± 15.4
- Median (Range)	47 (21-95)
Six months mortality	17 (23.9)

Data are presented as mean ± standard deviation or number (percentage)

admission. Mean 3MS score of patients was 49.3 ± 15.4 (Table 2).

The results of the second part of this study showed that the two groups (case and control) were comparable regarding their demographic data. The patients in case group were significantly older. The 3MS score was significantly lower in hyponatremic patients than normonatremic controls. The CSF glutamate was significantly higher in hyponatremic cases than normonatremic controls (Table 3).

Lower 3MS score in cases was inversely correlated with higher CSF glutamate (r = -0.4) as shown in Figure 2. Data are presented as mean ± standard deviation (SD), or number (percentage).

$P < 0.05$ was considered statistically significant.

4. Discussion

The main finding in this study was that hyponatremia is highly prevalent in the elderly patients with fractures around the hip above 70 years. Most patients were females. Additionally, the degree of hyponatremia was mild in 89.7% of the hyponatremic patients and moderate in 10.3%. Our study results (prevalence of hyponatremia) are equivalent to earlier reports by Indian authors, who reported hyponatremia in 45.6% and 47.9% of adults. [8, 9] A researcher found the frequency to be 58.8%. [10] Many studies have been done in western countries searching for this prevalence, but they found different results. Hoyle et al. noticed that hyponatremia was found in 18% of 103 elderly patients (mean age 82 y) who were admitted to a hospital geriatric assessment ward. An additional 24% became hyponatremic during the period of hospitalization. [11] In those countries the figures were 19% to 20.3% of elderly patients, the majority of them being female. The degrees of hyponatremia varied in different studies. [12, 13, 14]

Hyponatremia is an age-related complication. Geriatric patients are susceptible to dehydration due to various factors, including decreased body water content, less fluid intake, unwise use of diuretics, susceptibility for infections or a combination. At present, there is no biological marker to detect volume status and we solely depend on clinical assessment with uncertain accuracy in diagnosis, especially in geriatrics. [15] Clearly, the thirst sensation diminishes with age, which significantly impairs the ability to sustain homeostasis and increases dehydration risk. There is also a clear age-related decrease in maximal urinary concentrating ability, which also increases the risk for dehydration. Anti-diuretic hormone (ADH) release is not impaired with aging, but ADH levels are increased for any given plasma osmolality level, indicating a failure of the normal responsiveness of the kidney to ADH. The ability to excrete water is delayed in the old age personnel. Other changes in renal anatomy and physiology that increase the elderly patient's exposure to alterations of water imbalance include decreased renal mass, cortical blood flow and glomerular filtration rate, as well as impaired responsiveness to sodium balance. [16]

Table 3: Demographic, clinical, and laboratory of case and control groups

Variable	Case group 1 (n = 18)	Control group 2 (n = 10)	p-value
Age (y)	75.39 ± 4.9	71.5 ± 2.3	0.026
Comorbidities			
- Hypertension:	3 (16.7)	3 (30)	0.733
- Diabetes:	2 (11.1)	0 (0)	0.744
Ejection fraction %	63.67 ± 4.5	67 ± 4.6	0.334
Admission Na+ (mmol/L)	132.7 ± 1.8	138.6 ± 1.7	< 0.001
3M score	44.94 ± 5.61	61.60 ± 5.81	< 0.001
CSF glutamate (µmol/L) *	9.47 ± 1.37	5.79 ± 1.83	0.042
Six months mortality	5 (27.7)	1 (10)	0.540

Data are presented as mean ± standard deviation or number (percentage)

Our prevalence was high most probably due to hypovolemic hyponatremia as manifestations of dehydration were found in majority of patients and such results can be assumed to be due to very hot climate in the south of Egypt (Assiut). It is in contrast to western studies where the climate is mostly cold. A major influence of climate on the prevalence of hyponatremia in the elderly has been suggested. [17]

A report from India showed that the incidence of hyponatremia (< 120 mmol/L) was greater during the peak southwest monsoon season, indicating that high humidity and temperatures are the influencing factors. In Switzerland and Austria, it was showed that the incidence of hyponatremia (< 135 mmol/L) was significantly enhanced during the hot weather times. [18] Hyponatremia in female gender can be assumed by many mechanisms. Estrogen and progesterone reduce the function of the Na^+-K^+-ATPase, which normally has an important function in the extrusion of sodium from cells during the development of hyponatremia. [19]

The age-related decrease in total body water (relative and absolute) predisposes such group of patients to water imbalance. Average healthy 30-40 y old persons have a total body water content of 55 to 60%. By age 75 to 80 y, the total body water content mostly decline to 50% or more. [16] I

n our study, the hyponatremic patients were significantly older than the normonatremic patients. Within the last decade, mild chronic hyponatremia was believed to be associated with little neurologic dysfunction e.g. attention deficit, gait disturbances, and falls and this is supposed to occur more in older age. [20] Kristen L. et al., detected the decline of cognitive function in hyponatremic patients by the Trails B test rather than 3MS score. Their findings were the first to demonstrate an independent relationship between lower serum sodium and cognitive deterioration in generally healthy, community-dwelling older men. [21]

We investigated the CSF glutamate as a mechanism of central effects of hyponatremia; comparison was made between normonatremic with hyponatremic patients regarding serum sodium, 3MS score, and CSF glutamate. We aimed to find any correlation between cognitive status assessed by 3MS score and CSF glutamate as a biomarker for hyponatremia.

CSF glutamate of the hyponatremic group was shown to be elevated compared with that of the controls. In this regards, Haruki F et al. found higher extracellular glutamate concentration in the hippocampus of the chronically hyponatremic rat compared with that of normonatremic rats. An elevated glutamate was found to induce early excitatory neuronal death in hippocampus and the neocortex and behavioral learning dysfunction. Additionally, excessive ambient glutamate induce

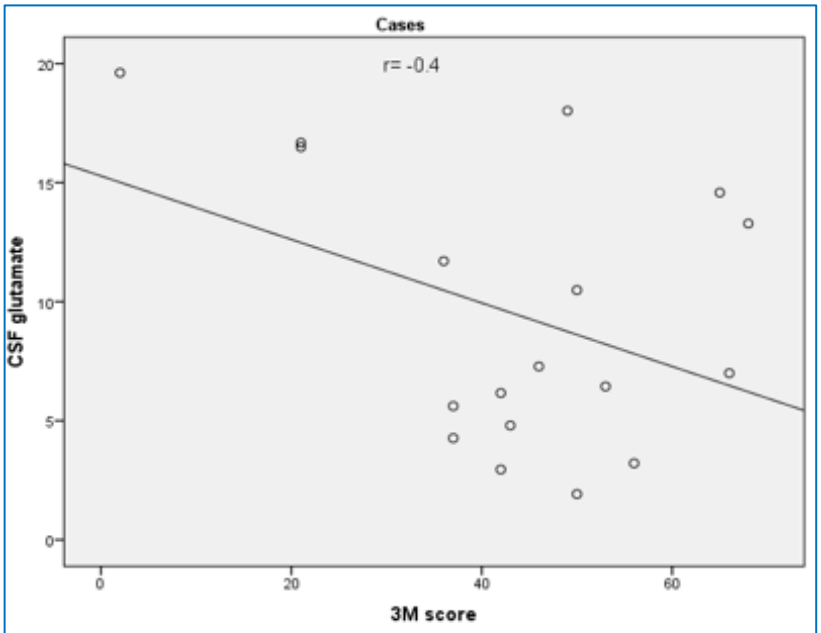

Figure 1: Correlation between CSF glutamate & 3M score

further stimulation of N-methyl-D-aspartate (NMDA) receptors leading to long-term potential impairment. [22] Brain cells are very sensitive to changes in osmolarity caused by hyponatremia. The assumed mechanism by which hyponatremia may contribute to cognitive impairment is the hypoosmolality astrocyte swelling. Hypoosmolality induces the release of excitatory neurotransmitters e.g. glutamate, and this may explain the neuronal dysfunction or injury. [21]

Teichberg V and coworkers mentioned that excessive brain glutamate rise may change its role as interneuron messenger onto neuronal toxin. The study mentioned that intraneuronal glutamate concentration is 10,000 times greater than its extracellular level. When a neuron senses the presence of too much extracellular glutamate in the vicinity; it turns on special pumps to uptake glutamate back in. This protective pumping mechanism works optimally if glutamate levels remain within the normal range. In case of cellular damage, liberation of high amounts of glutamate abolishing such protective reuptake function of the undamaged cells. Very high glutamate does not kill the neuron directly; however, it excessively excites the cell, opening cellular pores, and entry of large amounts of substances that are normally permitted to enter only in restricted quantities. [23]

As mentioned above, excessive glutamate release can be toxic to the brain and has been correlated with some neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. [24] In subjects without dementia, glutamate and glutamine are significantly and inversely correlated with the Mini-Mental State Examination score. [25, 26]

This denotes that changes in CSF glutamate levels delicately correlate with sub-clinical decline in cognitive function, and thus measurement of CSF glutamate may assist as a biomarker of subtle cognitive variations. This can be a good utility for early detection of pre-clinical dementia; hence proper initiation of preventive strategies prior to overt cognitive deterioration. [26]

Finally; the precious brain neurons that not easily regenerate die from this hazardous glutamate storm as a consequence of hyponatremia that can be easily prevented, detected and corrected. Sodium is a precise element in our body that seems to be cute and changes in can be neglected but the reverse is the fact; there is a close relationship between sodium and the brain, changes in sodium level are directly reflected on the brain.

5. Limitations

We suggest further studies with higher number of patients to find correlations between serum sodium, CSF glutamate, and 3MS scores. Radio-immunoassay determination of glutamate is less sensitive than high liquid chromatography, but this is the first look at changes in level of CSF glutamate and its correlation with cognitive function. Larger study group is needed to confirm our results.

6. Conclusion

Osteoporosis and hyponatremia are two major morbidities exposing the elderly, and leading to fractures around the hip. Osteoporosis is the predisposing cause for fractures around the hip in elderly while hyponatremia is a precipitating cause leading to attention deficit and falls.CSF glutamate levels are significantly and inversely associated with the 3MS scores in hyponatremic patients which rises a possibility of using it as a biomarker for neuropsychiatric disorders.

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8. Conflict of interest

Authors have no conflict of interest.

9. Data availability

Numerical data related to this study is available with the corresponding author.

10. Authors' contribution

All authors took part in the concept, conduct of the study, data collection, statistical analysis, literature search and the manuscript writing and editing.

11. References

Sandhu HS, Gilles E, DeVita MV, Panagopoulos G, Michelis MF. Hyponatremia associated with large-bone fracture in elderly patients. Int Urol Nephrol. 2009;41(3):733-7. [PubMed] DOI: 10.1007/s11255-009-9585-2

Hoorn EJ, Liamis G, Zietse R, Zillikens MC. Hyponatremia and bone: an emerging relationship. Nat Rev Endocrinol. 2011 Oct 25;8(1):33-9. [PubMed] DOI: 10.1038/nrendo.2011.173

Boddaert J, Raux M, Khiami F, Riou B. Perioperative management of elderly patients with hip fracture. Anesthesiology. 2014 Dec;121(6):1336-41. [PubMed] DOI: 10.1097/ALN.0000000000000478

Guerado E, Sandalio RM, Caracuel Z, Caso E. Understanding the pathogenesis of hip fracture in the elderly, osteoporotic theory is not reflected in the outcome of prevention programmes. World J Orthop. 2016 Apr 18;7(4):218-28. [PubMed] DOI: 10.5312/wjo.v7.i4.218

Aicale R, Tarantino D, Maffulli N. Prevalence of hyponatremia in elderly patients with hip fractures: a two-year study. Med Princ Pract. 2017;26(5):451-455. [PubMed] DOI: 10.1159/000480294

Am Soc Nephrol. Elderly can blame fractures and falls on low sodium; 2010. [FreeFullText]

Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987 Aug;48(8):314-8. [PubMed]

Kaeley N, Akram M, Ahmad S, Bhatt N. Hyponatremia in elderly – its prevalence, aetiology and outcome. Ann Int Med Den Res. 2017;3(2):ME16- ME19. [FreeFullText]

Dash SC, Sundaray NK, Rajesh B, Pagad T. Hyponatremia in elderly in-patients. J Clin of Diagn Res. 2019;13(2):OC01-OC04. DOI: 10.7860/JCDR/2019/39957.12554

Robin D, Manjunath D, Roshan D. Prevalence of hyponatremia in elderly patients admitted with fracture neck of femur. IOSR J Dent Med Sci. 2017;16(07):107-8. DOI: 10.9790/0853-160702107108

Hoyle GE, Chua M, Soiza RL. Prevalence of hyponatremia in elderly patients. J Am Geriatr Soc. 2006 Sep;54(9):1473; author reply 1473-4. [PubMed] DOI: 10.1111/j.1532-5415.2006.00872.x

Rocha AFB, Sá MVBO, Elihimas Junior UF. Hyponatremia in elderly patients with fragility fractures of the proximal femur: a cross-sectional study. J Bras Nefrol. 2019 Oct-Dec;41(4):518-525. [PubMed] DOI: 10.1590/2175-8239-JBN-2019-0019

Boyer S, Gayot C, Bimou C, Mergans T, Kajeu P, Castelli M, et al. Prevalence of mild hyponatremia and its association with falls in older adults admitted to an emergency geriatric medicine unit (the MUPA unit). BMC Geriatr. 2019 Oct 15;19(1):265. [PubMed] DOI: 10.1186/s12877-019-1282-0

Jain AK, Nandy P. Clinico-etiological profile of hyponatremia among elderly age group patients in a tertiary care hospital in Sikkim. J Family Med Prim Care. 2019 Mar;8(3):988-994. [PubMed] DOI: 10.4103/jfmpc.jfmpc_32_19

Rafiq MFA. Hyponatremia still remains largely undiagnosed and untreated. Anaesth Pain Intensive Care. 2017;21(1). [FreeFullText]

Kugler JP, Hustead T. Hyponatremia and hypernatremia in the elderly. Am Fam Physician. 2000 Jun 15;61(12):3623-30. [PubMed]

Giordano M, Ciarambino T, Castellino P, Malatino L, Cataliotti A, Rinaldi L, et al. Seasonal variations of hyponatremia in the emergency department: Age-related changes. Am J Emerg Med. 2017 May;35(5):749-752. [PubMed] DOI: 10.1016/j.ajem.2017.01.018

Sasaki N, Aoki Y. Seasonal variation in the prevalence of profound hyponatremia (< 125 mmol/l) in patients on admission to an acute hospital in Japan. Proceedings Singapore Healthcare. 2019:211-213. DOI: 10.1177/2010105819839373

Rosner MH, Kirven J. Exercise-associated hyponatremia. Clin J Am Soc Nephrol. 2007 Jan;2(1):151-61. [PubMed] DOI: 10.2215/CJN.02730806

Gankam Kengne F, Decaux G. Hyponatremia and the brain. Kidney Int Rep. 2017 Sep 1;3(1):24-35. [PubMed] DOI: 10.1016/j.ekir.2017.08.015

Nowak KL, Yaffe K, Orwoll ES, Ix JH, You Z, Barrett-Connor E, et al. Serum sodium and cognition in older community-dwelling men. Clin J Am Soc Nephrol. 2018 Mar 7;13(3):366-374. [PubMed] DOI: 10.2215/CJN.07400717

Fujisawa H, Sugimura Y, Takagi H, Mizoguchi H, Takeuchi H, Izumida H, et al. Chronic hyponatremia causes neurologic and psychologic impairments. J Am Soc Nephrol. 2016 Mar;27(3):766-80. [PubMed] DOI: 10.1681/ASN.2014121196

Vikhanski L. Protecting the brain from a glutamate storm. Dana Found. 2007. [FreeFullText]

Li CT, Yang KC, Lin WC. Glutamatergic dysfunction and glutamatergic compounds for major psychiatric disorders: evidence from clinical neuroimaging studies. Front Psychiatry. 2019 Jan 24;9:767. [PubMed] DOI: 10.3389/fpsyt.2018.00767

Lin CH, Hashimoto K, Lane HY. Editorial: Glutamate-related biomarkers for neuropsychiatric disorders. Front Psychiatry. 2019 Dec 5;10:904. [PubMed] DOI: 10.3389/fpsyt.2019.00904

Madeira C, Vargas-Lopes C, Brandão CO, Reis T, Laks J, Panizzutti R, et al. Elevated glutamate and glutamine levels in the cerebrospinal fluid of patients with probable alzheimer's disease and depression. Front Psychiatry. 2018 Nov 6;9:561. [PubMed] DOI: 10.3389/fpsyt.2018.00561

