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Case Study

Gait Abnormalities in a Patient with the Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Case Studied with Gait Analysis

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ABSTRACT

Introduction: Hyponatremia, defined as serum sodium concentration <136 mEq/l, represents one of the most challenging clinical disorder in geriatric rehabilitative settings . It is associated with significant morbidity and mortality. Hyponatremia can be often followed by neurological symptoms caused by cerebral oedema and in severe hyponatremia, patients frequently experience balance disorder and a high risk of falls.

Materials and Method: We report the case of a female patient, followed after an accurate diagnostic work-up for a syndrome of inappropriate antidiuresis (SIADH). Hyponatremia was initially treated with hypertonic saline infusion and then with fluid restriction. In consideration of the poor response to fluid restriction, treatment with tolvaptan was started. The patient experienced walking problems and was evaluated with an EMG computed Gait Analysis before and after that sodium level was normalized.

Results: Gait analysis carried out highlighted neuromuscular instability with alteration of the time parameter and spatial postural deficit. Once corrected the hyposodiemia the patient showed a marked improvement in neuromuscular control with normalization of the temporal and spatial parameter of the step.

Conclusions: The clinical manifestations of the patient with SIADH are related to the severity of hyponatremia and the speed with which the sodium deficit is established. The criteria for the diagnosis of SIADH in a patient with hypotonic hyponatremia remain those established by Bartter and Schwartz in 1967. Our suggestions is so to monitor balance and gait disorders and perform serial measurements of urine and serum osmolarity during rehabilitation process in order to prevent unbalance and falling.

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1. Introduction

The syndrome of inappropriate antidiuretic hormone (SIADH) is a frequent cause of hyponatremia. Hyponatremia is defined as a reduction in plasma sodium values below 136 mEq/L [1]. This decrease has a profound impact from a clinical point of view. Hyponatremia is present in 15%-30% of hospitalized patients. Hyponatremia can be associated with reduced, normal, or increased plasma osmolarity [2]. The treatment of SIADH must include the underlying cause. With regard to hyponatremia, in cases where neurological symptoms are present, the treatment is based on the administration of hypertonic saline with 3% NaCl, which can be associated with loop diuretics. This type of treatment is usually interrupted when one of the following three conditions occurs: the patient becomes asymptomatic, sodium reaches values of relative tranquillity (>120 mEq/L, but according to some authors >125 mEq/L), when it is however obtained an increase in sodium of 20 mEq/L. A critical aspect is the speed with which hyponatremia is corrected. To avoid the risk of causing massive intracellular dehydration, up to the dramatic occurrence of pontine and extrapontine myelinolysis, it is necessary to avoid too rapid corrections of plasma sodium [3].

The patient with severe hyponatremia is critical and in constant danger of death. The aspects to be taken care of are therefore twofold: cardiotoxicity and neurotoxicity. Cerebral edema and compulsive crises can occur in the acute phase, even in less than 48 h with Na <120 mEq/L, and in marked chronic hyponatremia. Brain edema can cause compulsive crises and balance disorder with an essential risk of falls, bone fractures, and significant cardiac arrhythmias. In severe hyponatremia, patients frequently experience balance disorder and a high risk of falls [4]. SIADH can occur at any age [5, 6]. Its incidence depends upon various etiologies. The prevalence of SIADH was estimated to be 2500-3000 cases per 100000 individuals. The incidence and prevalence of SIADH, in particular, are less studied in the literature. Hospitalized patients with plasma sodium concentration <125 mmol/L show overall mortality of 28000 per 100000 patients. The incidence of SIADH increases with age. The prevalence and incidence of SIADH do not vary by gender. The prevalence of hyponatremia is higher in females than males [7]. There is no racial predilection to SIADH. The prevalence of hyponatremia in the United States has been estimated to be 1720 per 100000 individuals [8, 9].

2. Case Report

A 78-year-old female patient with hyponatremia was admitted to the Internal Medicine Ward of Rummo Hospital in Benevento (Italy). She was received an accurate diagnostic work-up, and a diagnosis of syndrome of inappropriate antidiuresis (SIAD) was made according to the criteria established by Bartter and Schwartz in 1967 [10]. In general, in cases where neurological symptoms are present, treatment is based on administering hypertonic saline solution with 3% NaCl, which can be administered with loop diuretics. This type of treatment is usually interrupted when one of the following three conditions occurs: the patient becomes asymptomatic, sodium reaches values of relative tranquillity (> 120 mEq/L, but according to some authors> 125 mEq/L), when it is however obtained an increase in sodium of 20 mEq/L [6, 7]. In consideration of the poor response to fluid restriction, treatment with tolvaptan was started. During the days of hospitalization, derangement of coordination, weakness of the muscles of the lower extremities, and inability to walk, along with drowsiness, disorientation, and dysarthria, occurred. The patient was experiencing walking problems. She was evaluated with a superficial EMG computed gait analysis [11-15] before and after that sodium levels normalization. Neurologists excluded central pontine myelinolysis [3], and a nuclear magnetic resonance was planned. Her mini-mental test result initially was 14 [1] (Figure 1).

After the intensive therapy (0.9% NaCl solution along with tolvaptan), improvement in clinical status occurred. During the hospitalization, arterial blood pressure and their parameters were normal, and no episodes of hypotension were recorded. Laboratory tests confirmed severe hyponatremia refractory to intensive sodium substitution, so the patient was treated with tolvaptan at 30 mg tablets (Figure 2). Tolvaptan is a drug that acts as a competitive, selective antagonist of vasopressin V2 receptors. It is used to treat hyponatremia associated with congestive heart failure or liver cirrhosis and ADH inappropriate secretion syndrome. After sudden insulation at 135 mEq/L of sodium, there was a marked improvement of the clinic with a score of 30 at MMES (Figure 3). To have an objective assessment of the disorders and the subsequent treatment of the hyponatremia, the patient was subjected to the examination of the step with gait EMG analysis to study kinematics, dynamics, and surface electromyography [14, 15] (Figure 4, 5, 6, 7).

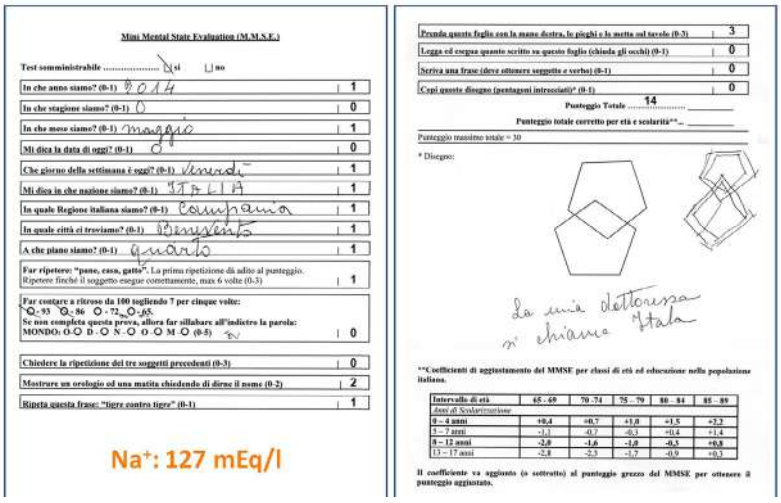

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Figure 1. Mini Mental Test pattien with Hyponatremia

3. Discussion

Patients with hyponatremia can divide into three categories based on extracellular fluid (ECF) volume. First is hypovolemic hyponatremia, where water and sodium are lost through the kidney or extrarenal losses (vomiting, diarrhea, diuretic drugs, extensive burns, cystic fibrosis). Second is euvolemic hyponatremia, where we usually find fluid retention with increased ECF and normal total sodium (due to different endocrine disorders such as adrenal insufficiency, SIADH, hypothyroidism, in the post-operative and from antidiuretic drugs). The final form is hypervolemic hyponatremia, where usually there is an increase in sodium content with a greater increase in edema and fluid accumulation in the interstitial compartment (ECF) (causes could be cirrhosis of the liver, kidney failure, congestive heart failure, nephrotic syndrome and excessive income of water) [1-9].

SIADH, described in 1957, represents the cause of 30%-40% of all hyponatremia and, together with treatment with thiazide diuretics, is one of the most frequent causes of hyponatremia in adults [1]. Therefore, it is essential to know the causes that can determine this condition, to make a correct diagnosis, and consequently establish an appropriate treatment. The first important line of distinction is given by the site where ADH is "inappropriately" secreted, which can be neurohypophyseal or ectopic. The latter condition is the most frequent cause of SIADH. It is associated with neoplastic diseases, such as small cell lung cancers, mesotheliomas, thymoma, carcinomas of pancreas, bladder, duodenum, prostate, or lymphomas. The causes that can determine

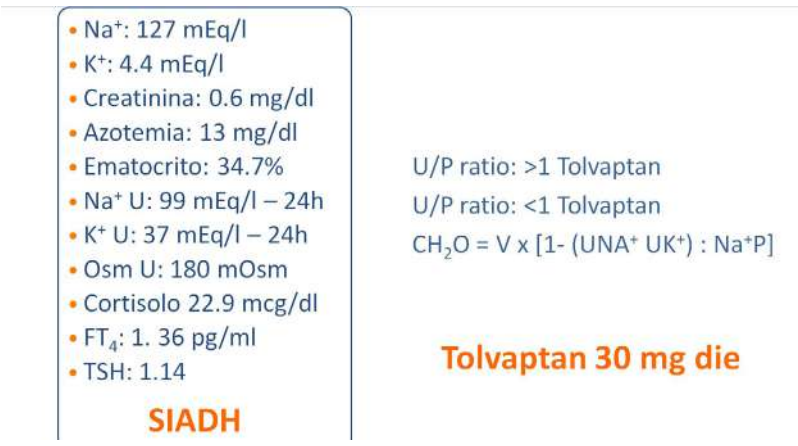

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Figure 2. Laboratory tests confirmed severe hyponatriemia refractory to intensive sodium supstitution

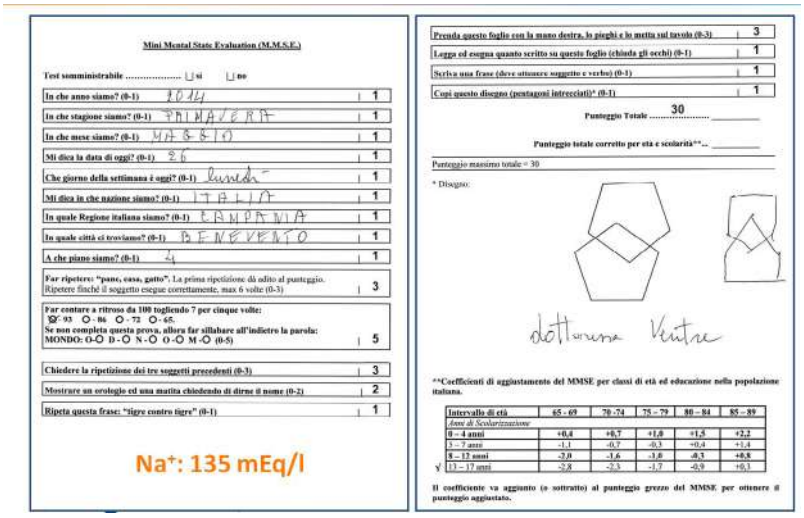

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Figure 3. After a sudden insulation at 135 mQ of sodium there was a marked improvement of the clinic with a score of 30 at MMES

inappropriate ADH secretion by the neurohypophysis are many. Numerous pathological conditions, for example, inflammatory or neoplastic, affecting the central nervous system or the respiratory system that can cause SIADH. It is essential to collect an accurate drug history of the patient. Numerous drugs can cause SIADH because they either increase the release of ADH (e.g., morphine, carbamazepine, haloperidol, tricyclic antidepressants, serotonin reuptake inhibitors, clofibrate, vincristine, vinblastine, bromocriptine, ecstasy among the drugs of abuse), or increase receptor sensitivity to the hormone (e.g., non-steroidal anti-inflammatory drugs, cyclophosphamide, chlorpropamide). Finally, other various situations can be associated with SIADH. For example, SIADH-related hyponatremia can occur following surgery, not just neurosurgical ones. Hyponatremia in these cases can be associated with stressful situations; pain stimulates the secretion of ADH. Blood loss and the fluid infusion can further aggravate the condition of hyponatremia in the post-surgical patient. Hyponatremia occurs in approximately 30%-40% of patients with AIDS [4, 5].

One of the possible causes of severe hypothyroidism in our rehabilitation patients could be the side effect of SSRI post-stroke therapy [16-18]. In a clinical setting, an immediate and correct examination of the patient is essential. In this type of gait disturbances where ambula-

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Figure 4. Gait temporal and spatial parameters before and after Na+ corrections.

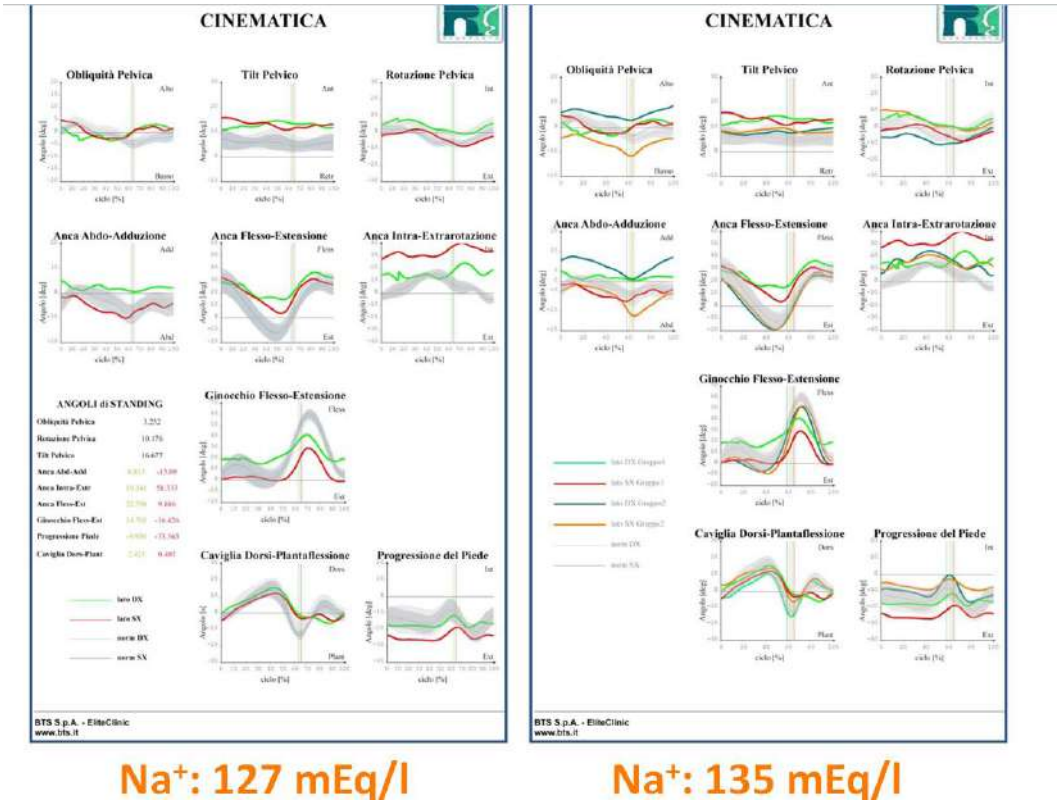

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Figure 5. KINEMATIC DATA before and after sodium corretcion

tory difficulties are evident, the clinical and neurological examination is very important, as are also several clinical tests such as the dynamic gait index (DGI) [19]. DGI has been validated for neurological and vestibular conditions and is used worldwide [20, 21]. Developed as a clinical tool to assess gait balance and fall risk, it evaluates not only usual steady-state walking but also walking during more challenging tasks [2, 16]. However, assessing the individual's ability to modify balance while walking in the presence of external demands is very difficult. Computerized gait analysis allows recording and quantifying a patient's walking over time to determine the ambulatory problems better.

In the last decade, a useful tool has become available to clinicians to evaluate the patients' disorders and follow them over time under the pharmacological and or rehabilitative program and assist the clinicians in selecting possible therapeutic adjustments.

In their recent paper, Lullo F. D'Addio G. et al. stigmatize how "biomedical technologies have an increasingly central role in the modern medicine," giving to the clinicians quantitative outcomes necessary on the choice of the right therapy [13]. In their paper, authors exhaustively focused on biomedical technologies used in the context of gait analysis describing the main ones used in the clinical practice about pathologies of neurologic, orthopedic, and rheumatic interest, underlining their importance in the clinical setting. They described all main systems for gait analysis: system with passive markers, stereophotogrammetry system, force, and pressure platforms, surface electromyography system, a system based on inertial measurement units" underling the importance of each in investigating different aspects [13]. Having the possibility to monitor the movement of the patient quantitatively leads to the possibility to measure the effects of medications, surgery, and rehabilitation accurately. It is proposed to record walking through the use of several integrated and interfaced instruments, each to investigate a different aspect of movement: video footage with multiple cameras to reconstruct movement in three spatial dimensions; force, and pressure platforms to measure the energy exchanged with the ground; and surface electrodes that allow simultaneous recording of the electrical activity of the muscle groups involved during the movement [13, 14]. The technique measures the kinematic variables (position, velocity, acceleration) and dynamic variables (forces). Several protocols are used to acquire a standardized and repeatable analysis; the most

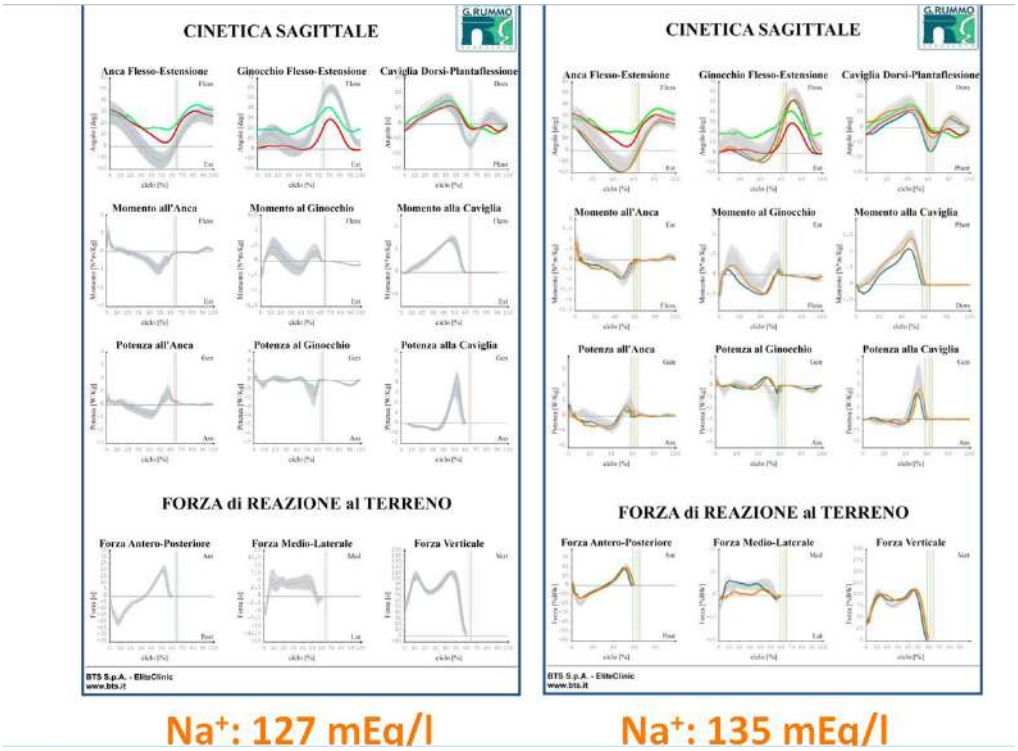

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Figure 6. KINETICS & Force reactions to ground . DATA before and after Na+ correction

common acquisition protocol is the Davis system [14], which includes the following steps. First, to perform anthropometric measurements: height, body weight, and bone segment parameters necessary to estimate joint centers (for example, the distance between the right and left anterior and upper iliac spines, the distance in the sagittal plane of the anterior iliac crests, and the great trochanter, etc.). Second, by positioning the marker on the body surface, to perform a static acquisition integrated with the anthropometric ones, it is possible to calculate the reference systems related to the bone segments and the position of the joint centers of the lower limbs. Finally, a dynamic acquisition of the motor acts of interest is carried out. From the three-dimensional coordinates of the markers, this system integrates the digital signals and reassembles a three-dimensional image of the subject. The time sequence of these images is the faithful reproduction of the kinematic motion of the joints, and it is possible to analyze the muscular electrical activity and force/energy produced by the muscle groups. These data assist the doctor in identifying the muscles most deficient or the activation pattern of the muscles during the gait [13, 14].

4. Results

In our case, the analysis was performed using the Elite system (ELITE 15, BTS, Milan, Italy) with 6 video cameras to acquire kinematic variables. Gait analysis results and time-distance parameters were collected and compared with kinetics data describing the forces that cause the movement (Figure 4, 5). Kinetic variables are important in gait analysis because they give information on what causes the movement of the joint or the limb, movement strategies, and neural compensation. Data shown in the figures represent the kinetic and kinematic profiles of our patient before and after sodium adjustment. The first results with Na+ 127 mEq/L showed an alteration of the temporal (increased velocity) and spatial (postural deficit) parameters of the step with global neuromuscular instability compared to normal parameter values (Figure 1). The results at baseline show that our patient tended to walk slowly with a longer gait cycle, a shorter step length, a longer double support time, and a lower cadence. Parameters obtained seem to confirm that during hyponatremia, she experienced a slower speed in an ataxic walking pattern associated with poorer muscle weakness. Static features were the extremely reduced walking unbalance and a persistent vertigo sensation. Several days after Na+ correction at 135 mEq/L,

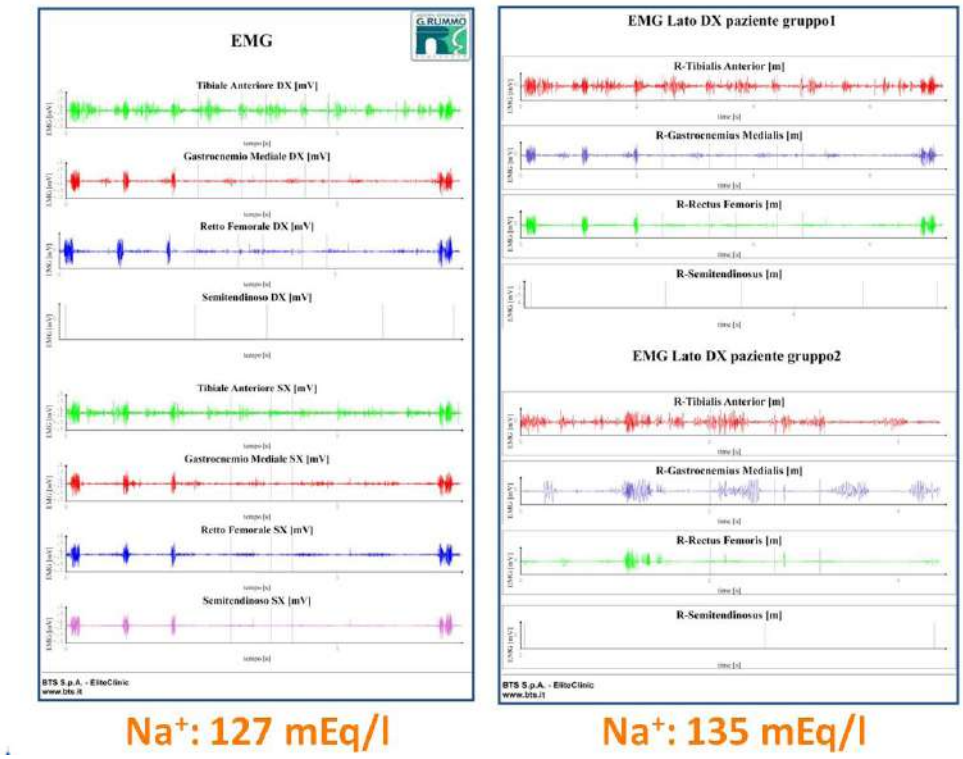

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Figure 7. EMG data before and after sodium correction

a new examination showed a sufficient normalization of the temporal and spatial parameters of the gait with a general improved neuromuscular control. The exam showed a general improvement in neuromuscular control, qualitative-quantitative performance of the lower limbs, and an apparent reduction in ambulatory difficulties with a clear reduction of the patient's risk of falling. With a good Na+ correction, during the swing, the hip joint showed, for example, different anterior pelvic tilt and a different and reduced pelvic rotation during walking. After hyponatremia correction at Na+ 135 mEq, the patient showed a marked improvement (comparing normal and pathologic parameter values) in neuromuscular control with normalization of the temporal and spatial parameters of the step. Clinically, the patient showed a significant improvement in neuromuscular control, qualitative and quantitative performance of the lower limbs, and a clear reduction in difficulties in ambulation and, therefore, a clear reduction in her risk of falling.

5. Conclusion

Hyponatremia has traditionally been defined as a plasma sodium concentration below 135 mEq/L. However, recent clinical studies correlating its values with those at risk of death have proposed reconsidering this cut-off point (e.g., suggesting sodium plasma level of 138 mEq/L). Severe hyponatremia is those with sodium levels lower than 125 mEq/L. Alongside the typical manifestations of the conditions that led to hyponatremia, for example, the signs of hypovolemia or the expansion of extracellular fluids, the neurological manifestations of hypotonicity of body fluids and, therefore, cerebral edema manifestations may dominate the picture. The more severe, the more rapidly the hyponatremia developed and the more marked it is [9]. Clinical manifestations are nonspecific and generally arise with sodium levels below 125 mEq/L and can present as generalized malaise, which can be associated with headache, lethargy, and dullness for sodium levels between 115 mEq/L and 120 mEq/L. For values below 115 mEq/L, there can be convulsions and coma. Recent studies show a direct correlation between hyponatremia and reduced bone density (bone contains about one-third of the body's sodium deposit), both in an animal model of SIADH and in humans, as shown by the evaluation of the data of the NHANES III (The Third National Health and Nutrition Examination Survey). Hyponatremia would stimulate the activation of osteoclasts with resorption of the bone matrix (Naticchia et al., Hyponatremia. G Ital Nefrol 2011; 28(3):305-313).

Clinical gait analysis offers objective documentation of the patient's status and helps in treatment planning and the pre/post-treatment comparison. Alterations in kinematic parameters have been extensively described in subjects with neurologic gait disturbances, in which sagittal plane alterations of pelvic mobility are generally interpreted as compensatory mechanisms to obtain better stride characteristics. In these patients, neurotoxicity, cerebral edema, compulsive crises, balance disorders with the risk of falls, fractures, and arrhythmias are very common medical risks. So in elderly patients, with or without SIADH, it is essential to monitor the possible hyponatremia and characterize it by its nature. The clinicians should monitor the patient's risk of falling and any frequent arrhythmias due to a frequent link between hyponatremia and cardiotoxicity (Figure 7).

Last but not least is the need to monitor elderly patients for an increased risk of osteoporosis as hyponatremia induces osteoporosis and is associated high risk of bone fractures [21, 22]. Gait, a computerized examination of the step, is objected through kinematic and kinetic parameters and shows how fragile the patient's neuromuscular equilibrium is and how much the step pattern and stability improves with a recovery of a suitable sodium plasma level. The message to take home is that the elderly subjects (potentially suffering from hyponatremia) who have sudden disorders of consciousness and walking may suffer from unknown hyponatremia and need appropriate correction based on the right cause. We must also consider that these patients are potentially at the risk of syncope and require careful monitoring with ECG for QTc and PR studies. The majority of cases of hyponatremia are seen in elderly hospitalized patients with several co-morbidities that may have additional contributing pathologies. This consequent hyponatremia is not frequently seen in a broad spectrum of malignant tumors, but it appears helpful to recall that several other illnesses cause SIADH as well [5]. Therefore, in an elderly patient with balance problems, the diagnosis of hyponatremia while using simple clinical and laboratory evaluations is complex and often challenging. Therapy should be modulated based on the symptoms and severity of hyponatremia. Vaptans (Vasopressin receptor antagonists) found in the eu- or hyper-volemic forms of hyponatremia and especially in SIADH is a possible indication that vasopressin level is not done routinely. In this regard, we suggest serial measurements of urine and serum osmolarity along with other laboratory parameters to conclude whether there is ectopic vasopressin secretion or not, to achieve a good clinical improvement as confirmed by gait analysis in our patient.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered and respected. The participant was informed of the purpose of the exams and research. A written consent form was acquired.

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This paper was extracted from clinical data of our gait analysis lab at Department Neuroscience.

Authors' contributions

R.C. and C.F follow patients admitted in the rehab ward and schedule clinical checks before and after clinical and computed analysis evaluation P.M and LDL did gait examinations and analysed technical results. VC and LDL wrote text. I.V. was the Internal Medicine specialist facing hyponatremia pharmacological therapy and the first clinical diagnosis. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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