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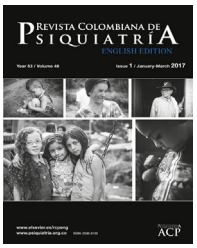

Case Report

Hyponatraemia associated with the use of quetiapine: case report☆

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ABSTRACT

Hyponatraemia is the most common electrolyte disturbance in the elderly. It can be asymptomatic or produce a spectrum of symptoms, particularly in the central nervous system, such as altered state of consciousness, lethargy, headache, seizures and gait disturbances, all of which are a common reason for consultation in this population. This condition has a high impact on the functionality of the patient given the need for multiple hospital stays, as well as on mortality. Its aetiology is multifactorial and its most common causes include low salt intake, chronic diseases such as kidney disease and heart failure, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is commonly caused by the chronic use of certain drugs, such as antidepressants, diuretics and antipsychotics, which are the most forgotten in clinical practice. The following clinical case presents the diagnostic approach of hyponatraemia and the importance of the medical history as a key tool to detect the aetiology of this clinical entity.

Hiponatremia relacionada con el uso de quetiapina: reporte de caso clínico

Palabras clave:
Hiponatremia
Anciano
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RESUMEN

La hiponatremia es la alteración electrolítica más frecuente en el anciano y puede ser asintomática o producir un espectro de síntomas, especialmente del sistema nervioso central, tales como alteración del estado de conciencia, letargia, cefalea, convulsiones y alteraciones en la marcha, los cuales son un motivo frecuente de consulta de esta población. Esta entidad tiene un alto impacto en la funcionalidad del paciente, pues requiere múltiples hospitalizaciones, e incluso en mortalidad. Su etiología es multifactorial; entre sus causas más comunes

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están la baja ingesta de sal, las enfermedades crónicas como la nefropatía y la insuficiencia cardiaca y el síndrome de secreción inadecuada de hormona antidiurética (SIADH), que a su vez se produce comúnmente por el uso crónico de determinados fármacos, como los antidepresivos, los diuréticos y los antipsicóticos, que son los más olvidados en el abordaje clínico. Se presenta en este caso clínico el abordaje diagnóstico de la hiponatremia y la importancia de la anamnesis como instrumento clave para detectar la etiología de esta entidad clínica.

Introduction

Hyponatraemia, defined as a serum sodium concentration <135 mEq/l, is the most common laboratory abnormality in elderly people. Its clinical presentation ranges from no symptoms or non-specific symptoms — such as muscle cramps, headache, gait abnormalities and lethargy — to significant neurological abnormalities, which may lead to seizures and coma due to cerebral oedema.[1] It occurs in approximately 15%–28% of the general population and has a daily incidence among hospitalised patients of 1%.[2]

Age-related changes in the kidneys promote the development of this condition, as they cause a decreased glomerular filtration rate; decreased urine osmolarity due to tubular changes; decreased serum levels of renin, antidiuretic hormone (ADH) and aldosterone and increased levels of natriuretic peptides; lowered sensitivity of thirst mechanisms; and greater difficulty with fluid intake due to physical and/or cognitive dysfunction.[2]

In addition, diseases that commonly co-occur with this condition in elderly people are heart failure, chronic kidney disease, pneumonia, neurological diseases, hypoxaemia, cancer and polydipsia.[3]

It is extremely important to recognise and treat this condition, as it is associated with increased one-year and 5-year mortality rates (due to requirements of orthopaedic procedures), longer hospital stays and increased healthcare expenditure.[2] Hyponatraemia in elderly people has also been linked to immobility, falls, cognitive decline, bone demineralisation and hip fractures.[3]

The most common cause is syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often caused by thiazide diuretics. However, many drugs are associated with this electrolyte imbalance, such as diuretics; antihypertensive drugs; antiepileptic drugs; non-steroidal anti-inflammatory drugs; and some psychiatric drugs such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and some antipsychotic drugs, especially first-generation ones.[4]

Owing to all of the above, a comprehensive approach should be taken to this condition in the geriatric population, since some diseases and drugs as well as renal ageing itself are linked to homeostasis and changes in electrolytes, such that hyponatraemia is a multifactorial entity in this age group.[4]

Due to population ageing, the number of people over 60 years of age is increasing, and, therefore, so are diseases and syndromes associated with this population group, including psychiatric diseases. Hence, the use of psychiatric drugs is increasingly common in elderly people. Their indications include psychotic disorders, delusional disorders, schizoaffective disorders, affective disorders, delirium and dementia.[5]

In dementia in particular, treatment of behavioural and psychological syndromes is based on non-pharmacological measures. However, around 70% of people over 85 years of age with dementia receive psychiatric drugs for a long period of time, depending on the seriousness and severity of their symptoms (risks for patient or caregiver safety), and the vast majority of these indications are off-label.[5] The drugs most commonly used to manage these symptoms include antipsychotic drugs, primarily for symptoms such as irritability, aggression and paranoid thoughts.[6]

Adverse effects of antipsychotic drugs include all those linked to the use of typical or first-generation agents, such as anticholinergic effects, hyperprolactinaemia, orthostatic hypotension, prolonged QT interval, sexual dysfunction and extrapyramidal symptoms.[7] Specifically, atypical agents are associated with weight gain, diabetes mellitus and metabolic syndrome. However, many adverse effects are class-dependent. That is why clozapine is associated with cognitive decline and seizures; risperidone and olanzapine are associated with gait abnormalities; somnolence is more common with clozapine, quetiapine and olanzapine; and extrapyramidal symptoms are more common with risperidone.[7]

In addition to these adverse effects, there are other reactions to atypical antipsychotic drugs, about which little is known, with associations based largely on case reports. Hyponatraemia is among them.

Below is a case report of hyponatraemia associated with the use of quetiapine.

Case report

An 83-year-old man had a history of major neurocognitive disorder in a severe stage secondary to multiple aetiologies (degenerative, vascular, traumatic and toxic). He showed behavioural symptoms of irritability, aggression, anxiety and insomnia, and was undergoing outpatient medical treatment with quetiapine 150 mg/day, sertraline 50 mg/day, memantine 20 mg/day and pregabalin 75 mg/day. Functionally, he showed a great deal of dependence in activities of daily living (Barthel index 35/100).

In addition to the above-mentioned history, the patient suffered from benign prostatic hyperplasia, being treated with prazosin 1 mg/day, and hypothyroidism, treated with levothyroxine 50 μg/day. He also had a history of resection of a pituitary macroadenoma in 2009, a severe traumatic brain injury with subdural haematoma and drainage in 2014, and alcoholism.

He was admitted due to signs and symptoms with an onset 1 h earlier consisting of unwitnessed loss of consciousness and loss of postural tone of approximately 5 min of duration, with subsequent mild traumatic brain injury and soft-tissue facial wounds. Accompanying his signs and symptoms were low blood pressure levels (75/40 mmHg). He was assessed by a home health care professional, who sutured his facial wounds and referred him to Hospital Universitario San Ignacio [San Ignacio University Hospital] for assessment and treatment.

On admission, the patient arrived in fair general condition, with borderline blood pressure levels, a mild traumatic brain injury with soft-tissue facial wounds and, as an incidental finding on heart and lung auscultation, rhonchi and abundant mobilisation of secretions in the context of his history of lung exposure. Laboratory testing on admission showed serum sodium 128 mEq/l, electrocardiogram with no rhythm abnormalities or acute findings accounting for his signs and symptoms, chest X-ray with nodular and micronodular opacities in the context of his chronic lung disease, simple computed tomography (CT) of the head with evidence of cerebral atrophy (not considered abnormal given his age) and changes subsequent to resection of his pituitary tumour. No acute haemorrhagic events were documented.

On admission, following evaluation by the emergency department, a decision was made, based on the patient's signs and symptoms, to rule out a pulmonary embolism component. Hence, CT angiography of the chest was ordered and yielded negative results for this condition.

In the course of his hospital stay, the patient underwent testing for syncope with an echocardiogram, Holter monitoring and carotid Doppler ultrasound. None of this showed any abnormalities that could explain his clinical picture.

Given his laboratory results, he was believed to have hypotensive syncope secondary to medication; therefore, he was taken off prazosin and put on dutasteride, and the psychiatry department decided to decrease his dose of quetiapine to 125 mg/day.

However, on discharge, the patient deteriorated due to the persistence of the electrolyte imbalances seen on admission. Again, his dose of quetiapine was decreased, follow-up laboratory testing of his electrolyte levels was done and his hyponatraemia persisted. Initially, it was decided to suspend sertraline, but the patient's sodium levels started to decrease to 120 mEq/l accompanied by an altered state of consciousness. At that point, the patient was believed to have symptomatic hyponatraemia, which required administration of several boluses of 3% hypertonic solution and suspension of quetiapine with sodium levels in follow-up testing of 132 mEq/l.

Following suspension of the antipsychotic drug, the patient presented deterioration of his behavioural symptoms — aggression, irritability and insomnia — whereupon he was given a dose of 75 mg of quetiapine. Follow-up testing found sodium levels of 119 mEq/l. The patient had another episode of severe acute hyponatraemia which required administering further boluses of hypertonic saline solution, suspending quetiapine and starting olanzapine for behaviour management.

At the same time, the patient was assessed by the endocrinology department to complement the hyponatraemia study. He had plasma osmolarity levels of 270 mOsm/kg, urine osmolarity levels of 462 mOsm/kg and urine sodium levels of 63.6 mOsm/kg. In view of these laboratory findings, the patient underwent further laboratory testing with TSH (1.34), free T4 (0.85) and baseline cortisol (6.02), which was in the grey area and did not account for the patient's clinical picture. These results were consistent with medication-induced SIADH and, following suspension of quetiapine, the patient's sodium levels gradually increased to 127 mEq/l. Once his behavioural symptoms were under control, it was decided to discharge the patient to his institution to continue his medical treatment with home visits by geriatrics and geriatric psychiatry. Days later, the patient was readmitted with new signs and symptoms of syncope, with suspected neurocardiogenic syncope; however, given his functional decline and severely impaired cognitive state, a decision was made to refrain from subjecting the patient to further testing and to give him symptomatic treatment. His sodium levels on readmission to the emergency department were 133 mEq/l.

Discussion

Hyponatraemia is a common condition in elderly people of multifactorial aetiology, and its main cause is SIADH. This syndrome is known to be an adverse effect of many drugs. Specifically, the psychiatric drugs most commonly associated with this condition are antidepressants, mainly SSRIs. In a review of the literature up to March 2013, Picker et al. found 147 studies that indicated that SSRIs — mainly fluoxetine, citalopram and escitalopram — caused a variable incidence of hyponatraemia (defined as serum sodium levels of 135 mEq/l), around 40%. This review found that the risk thereof increases in elderly people simultaneously taking diuretics, angiotensin-converting enzyme (ACE) inhibitors and laxatives, and that this increased risk is mediated by increased secretion by the hypothalamus of ADH, which, in turn, is mediated by serotonin receptors.[8] However, this incidence dropped by 0.06%–2.6% when the cut-off point was <130 mEq/l. A particularly interesting aspect of this review is the relationship that was seen between hyponatraemia and other antidepressants such as venlafaxine belonging to a high-risk group, whereas tricyclic antidepressants such as mirtazapine and duloxetine were found to entail a moderate risk of causing hyponatraemia.[8]

With respect to antipsychotic drugs, since 1970, it has been known that there is a link between thiothixene or haloperidol and fluid retention, hyponatraemia and decreased urine concentration. However, little is known about atypical antipsychotic drugs.[9] In a review by Meulendijks et al.[9] of 94 publications, most (91 case reports) found a possible relationship (around 80%) or probable relationship (19%). Of these, 47% improved following suspension of the antipsychotic drug. In addition, unlike that which happens with SSRIs, hypona-

traemia did not improve following dose reduction, and could present even weeks after having started treatment.[9]

Furthermore, a review by El-Safi et al.[10] on the safety of quetiapine in older adult patients found the most common adverse effects to be central nervous system adverse effects, orthostatic hypotension, dry mouth, weight gain and constipation. Just one case report of hyponatraemia associated with SIADH was found.

There are several theories as to why these medicines end up causing hyponatraemia. It is believed that their serotonergic activity causes them to act as a non-osmotic stimulus for ADH secretion by blocking or hypersensitising D2 dopamine receptors.

Conflicts of interest

The authors have no conflicts of interest to declare.

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