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CLINICAL CASE

Neurogenic orthostatic hypotension after diabetic ketoacidosis in a Mazahua patient

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Abstract

Introduction: *Diabetes is a significant worldwide health issue. In Mexico, it was described as the second major cause of death, affecting 12.8 million individuals. In the Mazahua Indian communities, the incidence of diabetes is 20% higher than in other indigenous communities nationwide. The prevalence of neurogenic orthostatic hypotension (OH) and autonomic failure in these patients is unknown.* **Case description:** *A 56-year-old female with diabetes who developed neurogenic OH after a diabetic ketoacidosis episode.* **Conclusions:** *Recognition of neurogenic OH in hospitalized patients will help address the early diagnosis and assessment of autonomic failure.*

Keywords: *Neurogenic orthostatic hypotension. Diabetes. Autonomic failure. Hospitalized patients.*

Introduction

Diabetes is a common chronic disease worldwide. In Mexico, a recent study by Bello-Chavolla et al.[1] showed that 12 million individuals suffered from the disease. The acute complications related to diabetes received treatment in the emergency department (ED) of the second level of attention hospitals. The naive indigenous populations in Mexico represent 6% of the total population[2]. According to the study of Esparza-Romero et al., the highest prevalence of diabetes was reported among the Mixtec population from Baja California (26.2%) and the Yaquis population from Sonora (18.3%).

Mazahua Indian communities in the north of Mexico State have a notably high incidence of diabetes compared to other indigenous groups nationwide. The study by Conzuelo-González and Vizcarra-Bordi found that 20% of this community had diabetes with chronic complications and frequent acute decompensation episodes, even the most common cause in the emergency rooms of public hospitals in these areas[3].

Neurological complications of diabetes have been well described in Mexican patients; however, the autonomic dysfunction related to small fiber neuropathy has yet to be thoroughly researched in the indigenous Mexican population, and the prevalence of efferent baroreflex failure is unknown[4]. Patients with diabetic autonomic neuropathy exhibit efferent baroreflex failure, deficiency in plasma catecholamine release, and a loss of post-ganglionic sympathetic neurons, resulting in the denervation of the peripheral arterial vasculature and

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showing clinical features such as orthostatic hypotension (OH), supine nocturnal hypertension, and post-prandial hypotension.

Autonomic failure leads to a poor response in blood pressure to the gravidity challenge, such as arising from lying down to a standing position, resulting in OH. OH symptoms vary, with mild and non-significant features as light-headedness, dizziness, and coat-hanger pain to prodromic fainting symptoms or syncope, or in extreme cases, hypovolemic shock[6]. Severe cases often do not respond well to conventional treatments used in hospitalized patients.

Case presentation

A 56-year-old female was admitted to the ED due to 5 days of drowsiness, fever, and back pain. She has been living with diabetes for 20 years, with non-compliance to treatment and poor blood sugar control.

She had dry mouth, confusion, and an elevated respiratory rate (32/min). The blood pressure in lying down was 70/40 mmHg, with a heart rate of 92 bpm, and a temperature of 101.1°F (38.3° ˚C). She was diagnosed with severe diabetic ketoacidosis (DKA) and community-acquired infectious pyelonephritis. She began IV fluids, norepinephrine infusion, electrolyte replacement, insulin infusion, and antibiotic therapy. The DKA resolved in 24 h, and she continued her treatment in the hospital. After 10 days of antibiotics (day 11), her follow-up laboratory serum tests were normal. However, she did not tolerate weaning norepinephrine because her blood pressure dropped to 60/30 mmHg and worsened when she moved from a lying to a sitting position. She had experienced brain fog, blurred vision, profuse sweating, drowsiness, and fainted when attempting to sit up on two occasions. These symptoms persisted while she was lying down, and her blood pressure slowly rose.

Furthermore, she had blurred vision, dizziness, light-headedness, drowsiness, and fainted after she was eating high-carb meals. Her blood pressure dropped to 60/40 mmHg with a heart rate of 55. She received an IV single bolus of Hartman solution (250 cc) and was allocated to the Trendelenburg position. The norepinephrine infusion was increased up to 0.65 mcg/kg/min. She remained on norepinephrine infusion with periodic adjustments according to blood pressure levels. Moreover, she experienced a new episode of mental fog and fainting symptoms after consuming carbohydrate-rich meals, followed by a drop in blood pressure of 70/50 mmHg over the next 120 min. On the following, she experienced constipation, empty fullness after eating, bloating, nausea, vomiting, urinary urgency, frequency, and nocturia. In addition, her blood pressure levels at night showed a marked tendency to rise (Fig. 1).

We decided underwent her to new assessments to rule out differential diagnosis[7,8] (Fig. 2) and essay trials of treatment for improve her blood pressure levels[9] (Fig. 3). After a 48-day hospital stay, her blood pressure levels improved and reached a systolic BP of 90 mm Hg during the day, she was discharged at home.

Conclusion

Autonomic dysfunction in hospitalized patients is feasible using a conventional blood pressure monitor. We provide an assessment of the behavior in the BP using an orthostatic challenge to determine the delta systolic heart rate over systolic blood pressure ratio (ΔHR/SBP), which can help confirm neurogenic OH and guide the etiological approach. The blood pressure and the pulse should be measured every minute for 5 min in the supine position and 10 min in the standing position. Subtracting the last systolic blood pressure in the supine position from the systolic blood pressure at 3 min of upright position. Furthermore, it is necessary to do the same subtraction between the heart rate in supine and the heart rate at 3 min of standing.

The delta ΔHR/SBP ratio will be calculated by dividing the heart rate by the systolic blood pressure results. If the ratio is < 0.5, it strongly suggests a neurogenic OH. In the original study from Norcliffe-Kaufmann et al.[10], the ΔHR/SBP ratio was tested in patients with alpha-synucleinopathies such as multiple system atrophy (MSA), pure autonomic failure (PAF), Parkinson's disease (PD), Lewy bodies Dementia (LBD) in the tilt table testing, showing excellent sensitivity (91.3%) and specificity (88.4%) to distinguish between patients with neurogenic versus non-neurogenic OH (area under the curve = 0.96, $p < 0.0001$). If the delta ratio exceeds 0.5, it should address non-neurogenic causes of OH. Once a neurogenic OH diagnosis has been corroborated, the assessment can be focused, as we labeled in Figure 4. In addition, during the orthostatic challenge, we suggest taking catecholamine levels (norepinephrine, epinephrine, dopamine, vasopressin, and renin) in the supine and standing positions to discriminate pre-ganglionic or post-ganglionic autonomic failure. The algorithm reduces the number of etiologies, as Goldstein and Cheshire described[11]. Neurodegenerative central causes are the main etiology of pre-ganglionic sympathetic failure, such as MSA. Post-ganglionic etiologies are broad since peripheral neuropathies (metabolic, hereditary,

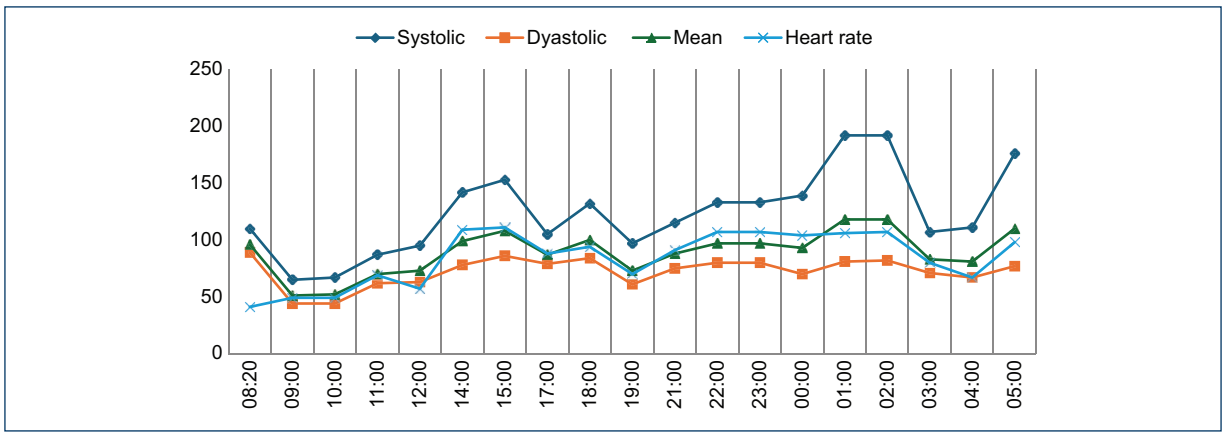

Figure 1. Blood pressure levels with conventional telemetry. The patient exhibited blood pressure lability during the day. She was unable to stand up and remained in supine and sitting down. She had episodes of post-prandial hypotension, supine hypertension, and one episode of fainting (day 15 post-DKA).

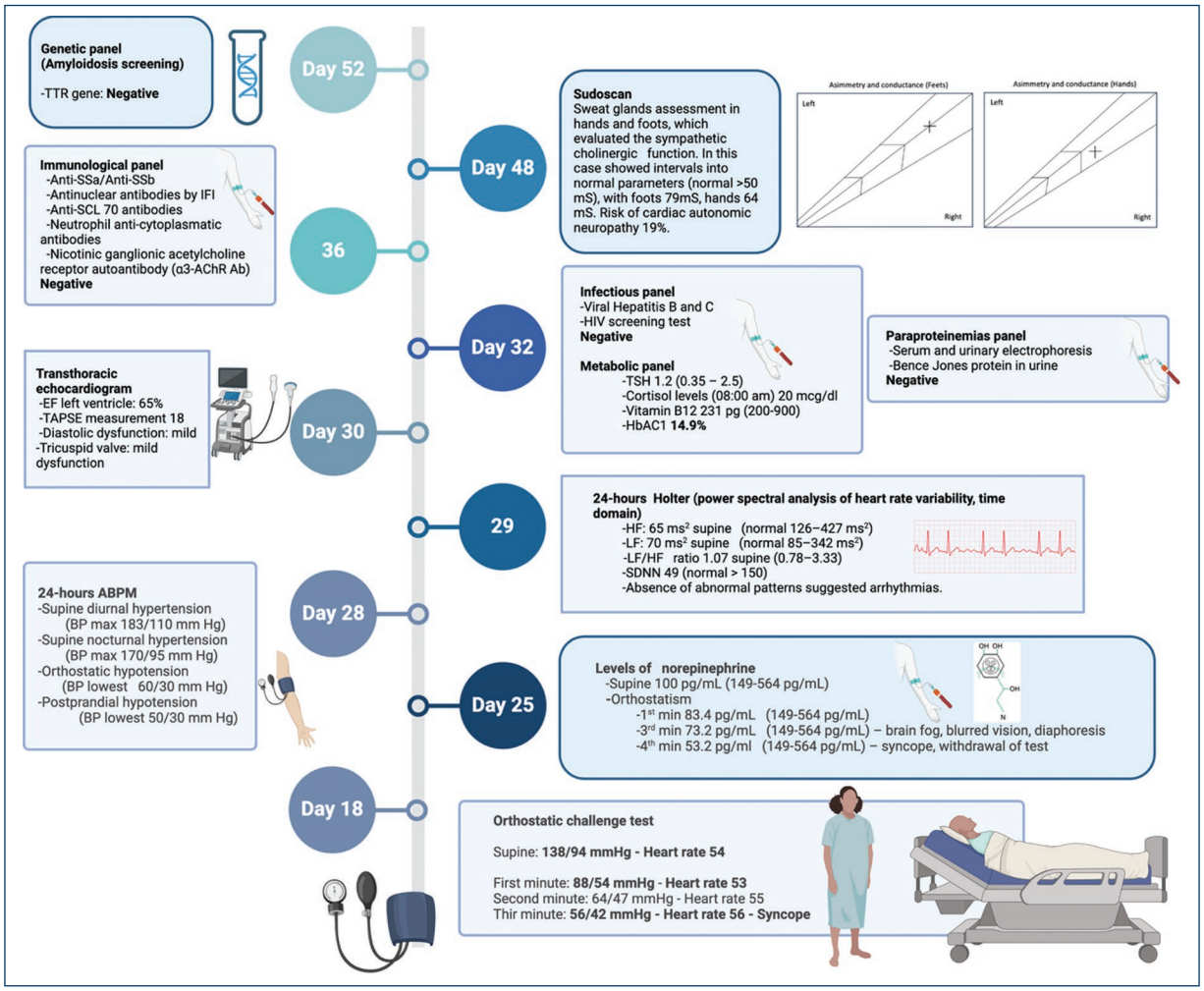

Figure 2. Timeline approach in our case.

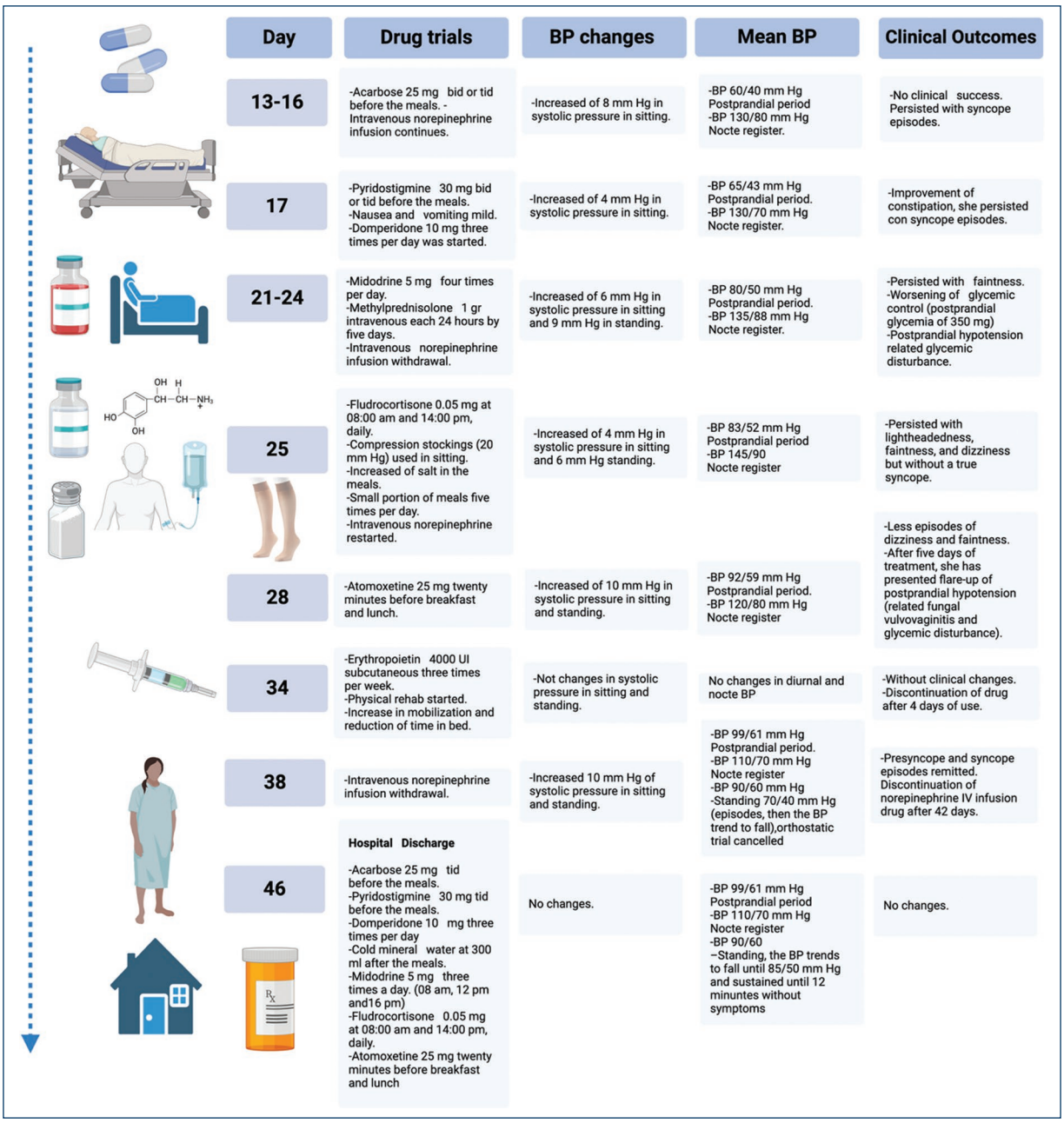

Figure 3. Timeline of medication trials tested in the patient.

autoimmune, paraneoplastic, etc.), or degenerative diseases such as PAF, PD, or LBD[12].

Denervation patterns in autonomic failure are clues for diagnosis. Can affect one, two, or all autonomic system divisions (sympathetic, parasympathetic, and enteric). The complete implication of the autonomic system is denominated pandysautonomia.

One cause of pandysautonomia is the autonomic autoimmune ganglionopathy (AAG), with monoclonal IgG antibodies against the subunit 3 of ganglionic acetylcholine receptors (α3-AChR Ab). The patients have a subacute or acute progression of autonomic symptoms, such as OH, supine hypertension, post-prandial hypotension, constipation, diarrhea, sexual dysfunction, bladder incontinence, frequency, and urinary retention. They can endorse anhidrosis, hyperhidrosis, temperature, skin color changes (limb acrocyanosis, Raynaud phenomenon), pupillary changes (Adie pupil) in weeks or months.

The α3-AChR Ab antibodies were described by Vernino et al in 1998[13]. The original study included

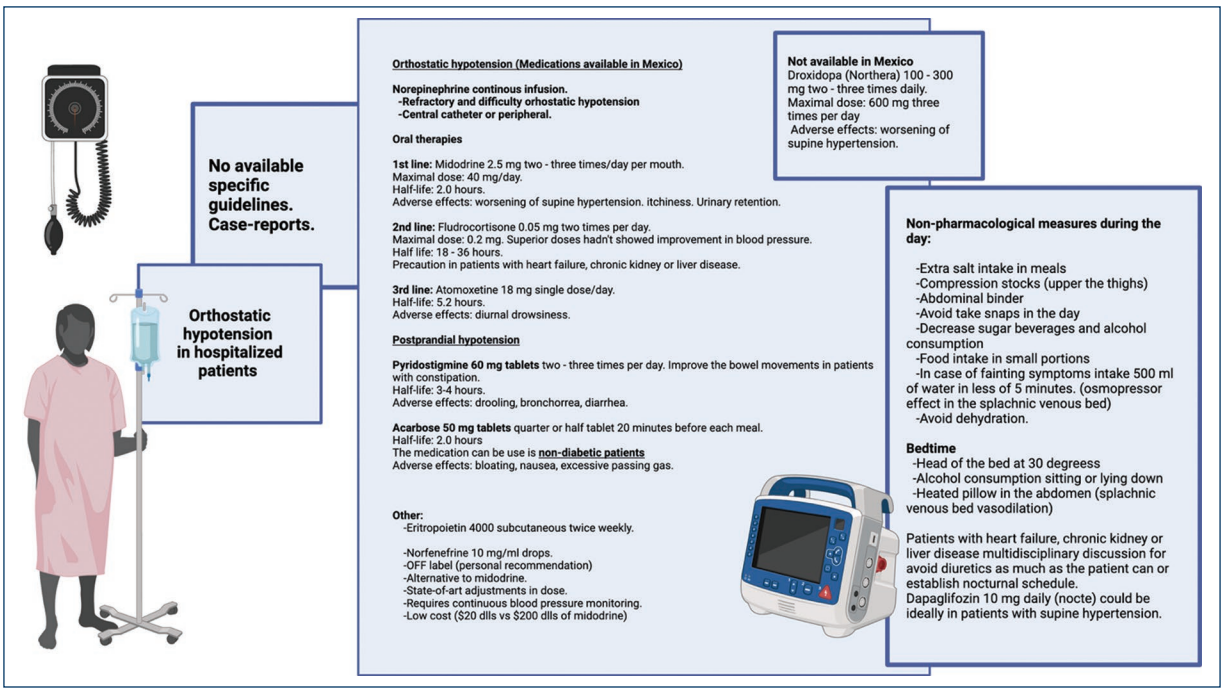

Figure 4. Therapeutic lines in orthostatic hypotension in hospitalized patients.

patients with alpha-synucleinopathies, diabetic neuropathy, idiopathic autonomic neuropathy, postural tachycardia orthostatic syndrome, idiopathic gastrointestinal dysmotility, and paraneoplastic autonomic neuropathy. All the patients exhibited antibody positivity, with the exception of patients with degenerative diseases (MSA, PD, PAF, LBD). That suggests the chronic inflammatory conditions can develop monoclonal antibodies in patients with high risk factors, such as rheumatological diseases (rheumatoid arthritis, systemic erythematosus lupus, myasthenia gravis, pernicious anemia, Sjogren syndrome, inflammatory intestinal disease, and systemic sclerosis). As the AAG has been considered a paraneoplastic syndrome, we should rule out occult neoplasia and follow up for at least 5 years.

There are case reports of AAG with isolated enteric nervous system damage, called gastrointestinal autonomic neuropathy[14]. The patients developed subacute motility disturbances in the upper or lower gastrointestinal tract (oropharyngeal dysphagia, thoracic dysphagia, gastroparesis, chronic intestinal pseudo-obstruction, constipation, and fecal incontinence) with a not clear etiology in the work-up and a positive serology for the α3-AChR Ab. The course of this entity will be monophasic, remission, or relapse-exacerbation (36 months), either or not therapeutic intervention.

There were case reports of patients with clinical features of AAG and negative α3-AChR antibody. In a converse fashion, we favor beginning treatment as soon as possible to stop the pathophysiological mechanism and hopefully avoid the augment. The treatment must be initiated with conventional immunosuppressor therapy described in the literature (high dose of intravenous methylprednisolone, intravenous immunoglobulin, azathioprine, mycophenolic acid, plasma exchange, rituximab, etc.), regardless of the serology status of the α3-AChR antibody[15,16].

We concluded the diagnosis of diabetic autonomic neuropathy for the evolution and improvement during hospitalization and post-discharge. However, the patient continues in vigilance because the seronegative status of the α3-AChR antibody didn't rule out the diagnosis of AAG. Regarding our patient's diagnosis, our discussion was the possible correlation between DKA and acute sympathetic failure. The relationship between acute exacerbations of diabetes (DKA and hyperosmolar hyperglycemic state) and autonomic dysfunction needs to be clarified. One theory suggests that the autonomic denervation could be due to microvascular regulation of the vasa vasorum, loss of myogenic reactivity, endothelial cell dysfunction, reduced high-quality angiogenesis, and a proinflammatory state[17]. This may be associated with the advanced

glycation of proteins on the basal membrane and glycocalyx. Moreover, the hyperglycemic environment may increase the prothrombotic state, leading to vessel obliteration and thrombosis of microcirculation in the sympathetic paravertebral trunks or vagal nerve endings.

Autonomic failure is a challenge for hospitalists, senior physicians, and residents. Neurogenic OH is the early clue of the different baroreflex failures. The subtle disturbances in a patient's blood pressure are related to positional changes (from supine to standing), abnormal circadian variations (where blood pressure does not follow the normal daily rhythm), and abnormal drops in blood pressure levels in the post-prandial period, which are cues to figure out the diagnosis. Multiple factors in critical care patients (adrenal failure, septic shock, heart failure, internal bleeding, antihypertensive medication, acute liver or kidney injury, metabolic acidosis, etc.) dismissed the neurogenic OH diagnosis. However, our threshold should be low to assess the blood pressure fluctuations. In the absence of recognized etiologies of hypotension, it should be attributed to neurogenic causes. We keep in mind that all systemic conditions lead to generalized hypotension and are non-related to position. The combination of OH and supine hypertension strongly suggests neurogenic OH, and we should emphasize the blood pressure and heart rate to address the diagnosis.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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