ABSTRACT

Objective: Major depressive disorder (MDD) represents the leading cause of mental disability worldwide. While relations between MDD and alterations to the cardiovascular system have been studied before, the autonomic dysfunction caused by the disease and the medical therapies involved during treatment has not been widely reported. Our case aims to prove such linkage exists and is a potent hazard during major operative procedures.

Methods: Studies have associated the disorder with a concomitant dysfunction of the autonomic nervous system, predisposing patients to hypertension. We present the case of a patient presenting with an intraoperative hypertensive spike that could be attributed to such a dysregulation of the autonomic system, in the absence of any other possible explanation.

Results: The observed intraoperative hypertensive spike was managed pharmacologically, and the patient did not experience any further hemodynamic instability or postoperative complications.

Conclusion: Our case tries to highlight a disregarded aspect of perioperative management for patients suffering from MDD.

Key words: Antidepressants, autonomic dysregulation, hypertension, MDD, perioperative care

Introduction

A wide range of patients, arriving for surgery, suffer from major depressive disorder (MDD), a leading cause of mental disability worldwide.[1] When it comes to preoperative evaluation, however, both psychiatric disorders and their treatment fail to be at the forefront of clinical decision making. The relationship between MDD and alterations of the cardiovascular system is a widely studied one,[2‑7] concluding that not only depression is an independent risk factor for hypertension but also that some sort of autonomic dysregulation favors an increased sympathetic activity with poor vagal control.[8] A case of a hypertensive crisis during a Whipple’s procedure on a patient with MDD led to a thorough investigation of the relevant literature in an effort to explore the probable cause. Approval and written informed consent was received from the patient.

Case Report

We present the case of a 68-year-old woman scheduled for a Whipple’s procedure. According to the patient’s history, she

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was receiving treatment for postthyroidectomy hypothyroidism. She was also treated with venlafaxine, lamotrigine, lithium, mirtazapine, lorazepam, and quetiapine for MDD. She had undergone surgery for several times in the past, without mentioning any adverse effects during general anesthesia.

Thyroid function tests, lithium levels, and blood test evaluation preoperatively were within normal values, as well as preoperative ECG and blood pressure, therefore rendering the patient at a low cardiac risk for surgery (revised cardiac risk index of 0.9%).

Following the psychiatrist’s recommendations, mirtazapine was discontinued 3 days before surgery, while 2 days before surgery, venlafaxine’s dose was reduced by a half. The day before surgery all medications were discontinued, with the advice to be restarted as soon as possible postoperatively.

Upon arrival at the operating room, the patient was connected to standard monitoring. For anesthesia induction, 200 mg of propofol, 150 mcg of fentanyl, and 60 mg of rocuronium were given intravenously. Videolaryngoscopy with CMAC was followed by a successful intubation with a 7 mm tracheal tube. For maintenance of anesthesia, sevoflurane 2% in oxygen–N₂0 1:1 mixture was chosen, aiming for a MAC of 1.

Immediately before induction, the high values of systolic arterial blood pressure were observed, ranging from 165 to 180 mm Hg, which were lowered to 120 mmHg immediately after propofol administration. Postintubation, systolic blood pressure was raised to 230 mmHg, with a concomitant heart rate elevation at 110 bpm.

At that point, repeated boluses of 50 mcg of fentanyl (550 mcg in total) were given, but since no respond was observed, a continuous infusion of glyceryl trinitrate of 100 mcg/mL was started immediately at a rate of 40–60 mL/h. Systolic arterial pressure remained at a high level of 180–190 mmHg. At that point, a continuous infusion of remifentanil (50 mcg/mL) at 8 mL/h was also added to ensure adequate analgesia. Nevertheless, no antihypertensive response was observed and incremental boluses of 30 mcg of clonidine (150 mcg in total) were administered, though without any effect. Bolus doses of morphine and dihydralazine were also given, up to a sum of 10 mcg of each drug but without any effect on blood pressure.

Finally, after a cumulative dose of 5 mg of phenotolamine, arterial pressure started to drop to 130 mmHg. Continuous infusions of glyceryl trinitrate and remifentanil remained throughout the rest of the procedure, which was concluded thereafter uneventfully. After resuming spontaneous ventilation, the patient was transferred to the ICU for monitoring. In the ICU, our patient was slightly hypertensive, with a mean BP of 160/85 mmHg; therefore, glyceryl trinitrate infusion was continued for several hours at a low rate.

Discussion

As the patient sustained good muscle relaxation, deep sedation, and well-titrated analgesia, her hypertensive crisis remained unexplained. One of the anesthesiologist's intraoperative main concerns is ensuring safe levels of blood pressure, in an effort to avoid end organ complications. Maintaining deep sedation, appropriate levels of neuromuscular blockade, and adequate analgesia throughout a surgical procedure guarantees that the source of hypertension is not related to anesthesia. Thorough control of anesthesia machine, pumps, and anesthetic gas supply, before starting a case, ensures that equipment failure is not a possible source of adverse reactions.

In our case, all of the above were meticulously checked both before induction and during the hypertensive episode as a problem-solving process of determining the cause of the crisis. Hypertension was not mentioned as part of our patient’s medical history. Having excluded essential hypertension, the thought of an occult pheochromocytoma occurred. However, the preoperative radiologic examination with computed tomography of the abdomen and the chest revealed no signs of adrenal malformation. Also, pathology analysis of the tumor extracted at the end of surgery revealed no signs of hormone-producing cells.

The possibility of a serotoninergic syndrome could not be ruled out due to our patient’s medication history. Attributed to an increased level of serotonin, the syndrome is characterized by a triad of altered mental status, autonomic dysfunction, and neuromuscular excitation. Venlafaxine (a serotonin norepinephrine reuptake inhibitor—SNRI), mirtazapine (a tetracyclic antidepressant), and lithium (an antiepileptic) drugs that were part of the patients antidepressive regimen, as well as fentanyl, and metoclopramide (both were administered intraoperatively) are all included in the vast list of drugs that can induce the syndrome. Apart from the patient’s unexplained tachycardia and refractory hypertension, which are common signs of serotoninergic syndrome, other symptoms relevant to the serotoninergic syndrome, like hyperpyrexia, were lacking.

Our patient’s treatment with quetiapine, an atypical antipsychotic, could be correlated with the appearance of
malignant neuroleptic syndrome. Nevertheless, our patient had neither hyperthermia nor muscle rigidity, which are necessary criteria for such a diagnosis to be made.\cite{16}

The lack of high temperature, clonus, rigidity, diaphoresis, hyperreflexia, and tremor, which are diagnostic symptoms according to either Hunter’s, Radomski’s, or Sternbach’s criteria, led us in ruling out both the above syndromes.\cite{10}

According to Scalco et al.\cite{8} a hyperactivity of the sympathetic system, proven through raised noradrenaline levels, along with reduced vagal tone due to an observed reduced heart rate variability, can both explain the relationship between depression and hypertension. Barton et al.\cite{17} reach a similar conclusion underlying a higher sympathetic outflow on patients with MDD. Several others studies regarding antidepressant medication and especially SNRIs\cite{4,5,7,18-20} demonstrate that this particular drug category can exacerbate the autonomic dysfunction of MDD, thus enhancing sympathetic activation and blood pressure rise. The core of autonomic dysfunction on patients with MDD seems to concern a shift toward sympathetic predominance resulting in higher sympathetic outflow \cite{20}.

Our suggestion, in terms of finding a cause for our patient’s unexplained hypertensive crisis, is an autonomic dysregulation attributed to the underlying mental disease, along with sympathetic activation, exacerbated by drugs such as SNRIs and by operational stress, which led to the refractory hypertensive episode. The fact that the only anti-hypertensive that controlled the crisis was phentolamine (a known nonselective alpha-adrenergic antagonist that halts sympathetic overreactivity), strengthens the hypothesis of a catecholamine excess on the patient.

### Conclusion

MDD is the most prevalent mental disorder worldwide, as well as the most disabling one. However, it seems that it fails to be a priority for an anesthetist, when handling a case, with other comorbidities present. It is important that the anesthesiologist, handling such patients, is aware of both the disorder and its pharmaceutical treatment. With this case, we want to highlight the importance of the relationship between the MDD treated with antidepressants and a latent autonomic dysfunction that under stressful events, like major surgery, can provoke an—difficult in handling— intraoperative hypertensive crisis.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts

| Author, Year | Study | Finding |
|--------------|-------|---------|
| Barton et al., 2007 | Observational study | A subset of patients with MDD present extraordinarily high sympathetic activity; SSRIs may reduce such activity along with cardiac risk |
| Hausberg et al., 2007 | Response to Barton et al. | They agree on the increased sympathetic activity; they question the cardiovascular risk and the contribution of antidepressants |
| Koschke et al., 2009 | Observational study | shift of autonomic balance toward sympathetic predominance, decrease in parasympathetic parameters and baroreflex sensitivity, and autonomic dysfunction is exacerbated by SNRI and to a lesser degree by SSRI treatment |
| Men et al., 2012 | Meta-analysis of prospective cohorts | Depression as an independent risk factor of hypertension |
| Scalco et al., 2005 | Review | increased prevalence of hypertension in depressed patients, possible underlying mechanism is a hyperreactivity of the sympathetic nervous system, and the use of antidepressants can interfere with blood pressure control of patients with hypertension |
| Light et al., 2009 | Cross-sectional study | antidepressants are being associated with both high diastolic and systolic blood pressures and hypertension |
| Dawood et al., 2009 | Response to light etc. | serotonin-norepinephrine reuptake inhibitors may be unsuitable for those with existing hypertension or vascular disease because of their tendency to raise blood pressure, this is not the case with all antidepressants |
| Alvare et al., 2016 | Systematic review and meta-analysis | reductions in heart rate variability (HRV) across psychiatric disorders; the above mechanism contributes to elevated cardiovascular risk in individuals with psychiatric disorders |
| Abo et al., 2019 | Review | antipsychotics, mood stabilizers, and some antidepressants have been independently associated with cardiometabolic events; increases in blood pressure have also been demonstrated in the use of antidepressants such as venlafaxine, duloxetine, and tricyclic antidepressants, which inhibit norepinephrine reuptake |
| Hu et al., 2019 | Observational study | the association between depression/anxiety and cardiac autonomic dysregulation does not result from a causal pathway or genetic pleiotropy; associations were likely confounded by the use of certain classes of antidepressants; antidepressant use (especially tricyclic antidepressants, selective serotonin, and noradrenaline reuptake inhibitors) is being related to an unfavorable cardiac autonomic activity across all waves |
will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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