Multiple anesthetic and obstetric challenges in a laboring patient with postural orthostatic tachycardia syndrome (POTS) : acquired hemophilia and a rare seizure disorder

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Abstract : A 24 year old female Gravida 4 para 0212 presented in preterm labor with three rare co-morbidities, postural orthostatic tachycardia syndrome (POTS), acquired hemophilia, and a reflex seizure disorder. POTS is a rare type of autonomic dysfunction characterized by severe tachycardia and orthostatic intolerance and can be exacerbated by labor and delivery and further aggravated by a neuraxial block. Acquired hemophilia or factor VIII deficiency is a rare form of hemophilia and unlike congenital hemophilia presents during adulthood and was diagnosed during the patient's previous pregnancy that resulted in a massive postpartum hemorrhage; requiring serial monitoring of Factor VIII activity and the availability of specific blood products during this admission. Reflex seizure disorder is a rare form of seizures and the patient's seizures were elicited by repetitive sounds, which is a major concern in a typical noisy labor and delivery suite setting with fetal and maternal monitoring. A careful and planned induction of labor was arranged after collaboration with the obstetric and hematologic services, which included maintaining a quiet labor environment and cooperation with the hospital's blood bank for the availability of blood products. Additionally, a tailored anesthetic during labor and delivery included low dose combined spinal epidural analgesia with emphasis on judicious epidural dosing limiting any hemodynamic changes while providing a near stress-free environment resulting in an uneventful outcome for both mother and baby.

Keywords : Postural orthostatic tachycardia syndrome ; reflex seizure disorder ; acquired hemophilia ; pregnancy ; combined spinal epidural analgesia.

Introduction

A 24 year old female was transferred to our care during the third trimester of her pregnancy, due to multiple medical problems including postural orthostatic tachycardia syndrome (POTS), acquired hemophilia, and reflex seizure disorder triggered by repetitive auditory stimuli (1-3). These three syndromes are rare manifestations of their respective generalized conditions. POTS is an uncommon form of autonomic dysfunction, acquired hemophilia is a rare form of hemophilia and reflex seizure disorder is a rare form of seizure disorders (1-3).

Case Report

The patient was seen in consultation when she was 35+5 weeks pregnant (Gravida 4 para 0212). Five years prior to admission, the patient was diagnosed with postural orthostatic tachycardia syndrome (POTS), following significant tachycardia (up to 200 beats per minute), without hypotension and syncopal episodes. Treatment included metoprolol 25 mg BID. Subsequently, she was diagnosed with a reflex seizure disorder elicited mainly by repetitive sounds (auditory triggers). The condition was treated with levetiracetam (Keppra^R, UCB Pharma, Inc., Brussels, Belgium), and lamotrigine (Lamictal^R, GlaxoSmithKline, Brentford, UK). The patient had been compliant with her anti-epileptic drugs (AEDs), and denied any seizure activity the previous year. Her last pregnancy three years earlier

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was remarkable for a massive vaginal hemorrhage twelve days postpartum that required an uterine artery embolization and intrauterine balloon tamponade. She received 9 units of packed red blood cells and multiple blood products. With no evidence of retained products of conception and a Factor VIII activity of 19%, she was diagnosed with acquired hemophilia (2). Thus, a plasma factor VIII level was obtained during her present admission.

She planned to avoid any anesthetic because her previous two labor anesthetics included a one-sided epidural block and a dense epidural block described as "someone sitting on her chest". She also requested to sit upright during labor as the supine position reminded her of the multiple syncopal episodes with POTS.

The patient was admitted to the hospital in preterm labor at 36+4 weeks with a cervical dilatation of 4 cm, 50% cervical effacement and at -2 station; she progressed to 7 cm dilatation until her contractions diminished. However, labor was induced at 37 weeks gestation due to her multiple medical comorbidities, her present stable condition, and a Factor VIII activity of 162% (normal range, 50-150%). Other laboratory data on admission included a hemoglobin level of 10.4, platelet count of 255,000 (150,000-450,000), and normal partial thromboplastin and prothrombin times.

Due to her history of reflex seizures triggered by repetitive noises, all audio alarms in her room were disarmed, including the fetal heart rate monitor during her induction with intravenous oxytocin. The morning of induction the patient received her scheduled dose of metoprolol. Moreover, due to POTS, intravenous 0.9% normal saline was selected and administered at a rate of 150 mL/hr in an attempt to ensure euvolemia. Vital signs included HR (95 to 105 BPM) and BP (130s/90s) over the following 6 hours, when the patient agreed to a neuraxial block. A combined spinal epidural (CSE) consisting of an 18ga 3 ½" inch Tuohy needle and a 27ga 4 11/16" Whitacre spinal needle (Durasafe^R, Becton, Dickinson and Co, Franklin Lakes, New Jersey) was performed with the patient in the sitting position. Fentanyl, 25 micrograms was administered intrathecally, followed by an epidural infusion via patient controlled epidural analgesia (PCEA) with bupivacaine 0.1% plus fentanyl 2 micrograms/mL at a rate of 6 mL/hour, with a 5 mL demand dose and a 20 min lock-out interval. Post CSE placement, vital signs included BP 138/94 and HR 79, and a visual analog pain score of 0 out of 10. The patient remained sitting upright after the CSE placement throughout labor as her blood pressure remained stable. Two

hours after CSE placement, she complained of pain, and she received two divided doses over 20 minutes totaling 12 ml of bupivacaine 0.125% plus fentanyl 50 mcg with excellent relief. Vital signs remained normal. A cervical exam revealed a completely dilated and effaced cervix and the fetal head had reached +2 station. The second stage of labor lasted 40 minutes with minimal pushing effort from the patient resulting in a spontaneous vaginal delivery of a viable female infant weighing 2,481 gm with Apgar scores of 8 and 9 at 1 and 5 min, respectively. On the second postpartum day her factor VIII activity had decreased to 73% activity, with some vaginal bleeding that subsided spontaneously and the patient was discharged home on the third postpartum day.

Discussion

With the history of POTS, acquired hemophilia, and an episodic seizure disorder, care of our patient during labor and delivery posed many challenges.

POTS is a type of autonomic neuropathy characterized by orthostatic intolerance, and noradrenergic activation in contrast to noradrenergic inhibition that characterizes diabetic autonomic neuropathy or Parkinson's disease and further differentiated from the common neuropathies by the lack of orthostatic hypotension (1,4). Pathophysiology includes neuropathy manifested by peripheral denervation resulting in venous pooling in the lower extremities and mesenteric vessels. Subsequently, there is decreased venous return and eventual cerebral hypoperfusion. Hyperadrenergic characteristics include palpitations, and elevated serum norepinephrine levels on standing (5).

The diagnosis of POTS is made by an increase in heart rate of 30 bpm (or 40 bpm in ages 8 to 19 years) or a heart rate of over 120 bpm, without associated hypotension within the first 10 minutes of standing (1,4). The diagnosis of POTS is complicated by a number of subtypes, broadly consisting of neuropathic, hyperadrenergic and deconditioned POTS and is commonly misdiagnosed as a panic disorder or severe anxiety (1). This difficulty in diagnosing POTS is exemplified by the mean time from onset of symptoms to diagnosis averaged over 10 years (6). The tilt table test, although not required, has been commonly used for diagnosis (5). Symptoms of POTS include fatigue, headaches, lightheadedness, palpitations, syncope, nausea, tremors, chest pain and shortness of breath. It is estimated that over one million patients in the United States may suffer from POTS due to misdiagnosis

of the syndrome (1, 4). The etiology of POTS is unknown however up to 50% of patients may have a viral prodrome and 25% of cases have a familial history (1). Our patient had neither condition prior to becoming symptomatic. The majority of patients (80%) are females and POTS presents most commonly between 15 and 50 years of age (1, 4, 6).

There is no definitive treatment for POTS; supportive measures include compression garments, exercise programs, increasing salt intake and avoiding dehydration (1, 4). Medications have been used in patients with more severe symptoms with some success and more commonly include beta blockers, fludrocortisone and midodrine (1, 4). For this reason, management during labor in our patient included administering an intravenous normal saline solution at a higher than normal maintenance rate (150 mL/hr), to avoid dehydration, along with continuing treatment with a beta-adrenergic blocking agent.

The hemodynamic changes during pregnancy can have conflicting effect on POTS; the increased blood volume may improve symptoms, while the increased heart rate may exacerbate the POTS symptoms. In a large retrospective study there were no long term effects of pregnancy on POTS (7). However, variable clinical courses of pregnant patients with POTS have been described, with either worsening unchanged or improved symptoms (6-10). A higher incidence of hyperemesis gravidarum and migraines were present in these patients (6, 8, 10). Initially, cesarean section was recommended in patients with POTS to avoid the pain and stress of labor and the Valsalva maneuver in the second stage of labor which could exacerbate the syndrome (5, 8). During the Valsalva maneuver, studies have demonstrated that patients with POTS have an increased splanchnic blood flow and decreased thoracic blood volume, with increased heart rate, including a 50% or greater decrease in pulse pressure compared to control patients (1, 5). Subsequent case series described successful labor and vaginal delivery with instrumentation (6, 9, 10).

Reports of patients with POTS undergoing anesthesia are limited. In addition to pregnancy, general and neuraxial anesthesia in patients with POTS can pose a challenge. Three of 13 non-obstetric patients undergoing general anesthesia had prolonged intraoperative hypotension requiring vasopressor therapy (11). With general anesthesia, drugs that induce tachycardia, such as ketamine and atropine, should be avoided. Phenylephrine is the preferred drug for treatment of hypotension as opposed to ephedrine due to its indirect sympathomimetic effects. Attention to perioperative fluid management as an adjunct to enhanced recovery after surgery (ERAS) is paramount to avoid hypovolemia in these patients.

The few reports that included anesthesia for labor and vaginal or cesarean deliveries were mostly performed with epidural anesthesia (6, 8, 9, 12, 13). Although a neuraxial block can alleviate most of the pain and stresses of labor, it also can result in hypotension in this tenuous hemodynamic syndrome. Moreover, a high sensory denervation level that is required in a cesarean section results in a near or total sympathectomy with ensuing hypotension and bradycardia (14). Because of its faster onset than epidural anesthetic, spinal anesthesia can lead to a greater decrease in blood pressure, rendering it less desirable. For a cesarean section, either an epidural anesthetic or a combined spinal epidural anesthetic (with an initial small local anesthetic intrathecal dose) can be titrated. This technique is preferred to a spinal and avoids the abrupt and marked decreases in blood pressure. However, a prophylactic intravenous phenylephrine infusion during spinal anesthesia can diminish its hypotensive effects (15). In contrast, a lower sensory denervation level in a laboring patient (and therefore a lower sympathetic level) is required for pain control with a neuraxial block and more easily maintains hemodynamic stability than the neuraxial block required for a cesarean section. Considerations in a laboring patient include early neuraxial catheter placement to avoid the stress of pain and limiting the local anesthetic dosage. Other anesthetic considerations with either mode of delivery include judicious use of epinephrine containing local anesthetic solutions, if needed, and indirect agents such ephedrine when treating hypotension to avoid the hyperadrenergic response.

With the abrupt onset of labor pain and reassurance of receiving a relatively low sensory block, our patient eventually opted for a neuraxial block. The neuraxial block consisted of a CSE with an intrathecal opioid alone to minimize the hypotensive effects that can occur even with the addition of small doses of intrathecal local anesthetics (16). Despite the orthostatic intolerance, our patient requested to remain upright for her neuraxial placement and throughout labor as tolerated, as she feared the supine position due to "finding herself on the floor" following her frequent syncopal episodes. Although performing a neuraxial block in the lateral position in patients with autonomic neuropathy would be the preferred position, we elected to perform the CSE

technique in the sitting position. This decision was not only based on the patient's request, but we felt that we could minimize any hemodynamic effects by eliminating the use of any local anesthetic bolus, intrathecal or epidural. Our CSE technique consisted of intrathecal fentanyl alone, which was immediately followed by an epidural infusion of a low concentration of a local anesthetic with an opioid, obviating the need of an epidural bolus dose and thus minimizing the risk of hypotension and a high sensory block.

Another consideration in patients with POTS, similar to cardiac patients, is to minimize the stresses of the second stage of labor by avoiding or reducing maternal pushing efforts or the Valsalva maneuver. Instead, passive descent of the fetal head should be considered and subsequently, an instrumented vaginal delivery can be performed, if needed. As noted previously, the Valsalva maneuver results in more pronounced hemodynamic changes in patients with POTS (1,5). Our patient had a relatively short second stage of labor requiring minimal pushing; this precluded the need for an assisted second stage of delivery.

As opposed to the more common inherited hemophilia which manifests early in life and involves hemarthroses, acquired hemophilia is rare and usually presents later in adult life due to antibodies that inactivate Factor VIII (2). Although pregnancy only accounts for less than 10% of the acquired hemophilia cases, younger females are prone to acquired hemophilia due to an increase in inhibitors in the postpartum period, manifested by postpartum hemorrhage, similar to our patient's previous history (17, 18). Acquired hemophilia, although rare, should be considered in the differential diagnosis of severe hemorrhage, along with a prolonged aPTT but with a normal PT, platelet count and fibrinogen level, differentiating it from disseminated intravascular coagulopathy (18). Although factor VIII activity was markedly higher than normal in our patient during labor, the greater concern was in the postpartum period. Interestingly, the patient's factor VIII activity declined from 162% activity prior to induction to 73% two days postpartum, resulting in transient vaginal bleeding. Treatment of acquired hemophilia includes des-mopressin acetate (DDAVP) or Factor VIII and in more severe conditions, treatment includes acti-vated prothrombin complex concentrate (aPCC), recombinant factor VIIa, plasmapheresis, or immu-nosuppressive therapy (2, 18).

Seizure disorders are present in less than 1% of pregnancies (3). Our patient had reflex seizures, a rare disorder that makes up only 6% of all seizures (19). The patient's underlying seizure activity can be confounded by pregnancy-related seizure activity associated with eclampsia, cerebral venous thrombosis and local anesthetic toxicity from an accidental intravascular injection.

The effect of pregnancy on seizure activity is variable however an increase in seizure activity may be related to increases in renal and hepatic clearance of drugs, and increased volume of distribution. Non-compliance can be a factor, as patients are concerned about potential fetal teratogenic effects of AED's, although the newer AEDs contribute to fewer fetal effects (3, 19). Management during pregnancy includes folic acid supplementation, as some AEDs decrease folic acid levels, increasing the risk of neural tube defects. Reflex seizures are rarely induced by auditory stimuli, as in our patient (3, 19). Seizure activity elicited by repetitive sounds was a concern in our patient from fetal monitors in the labor and delivery suite. A concerted effort was made to limit audible monitors in the patient's room during labor and delivery, although this practice must be supplemented with telemetry monitoring at the nurses' station and increased healthcare provider vigilance.

In summary, the management of our patient was complicated by competing issues and our treatment and care were designed to offset these concerns. Induction of labor was scheduled early due to her stable condition, and a neuraxial block was tailored to control the pain and stress of labor and delivery, while maintaining hemodynamic stability in a patient with autonomic dysfunction, specifically POTS. Other concerns involved pre-paration for a possible massive hemorrhage with specific blood products required for acquired hemophilia and maintaining a quiet environment in a typically noisy labor and delivery suite reliant on fetal monitoring in a patient with an episodic seizure disorder. Appropriate prenatal consultations and multidisciplinary involvement are paramount to ensure optimal care and controlled management of a high-risk obstetric patient with rare comorbidities.

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