Case Report

Myasthenia gravis and preeclampsia: Dot all the I’s and cross all the T’s

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Abstract

Although rare, the co-occurrence of myasthenia gravis and preeclampsia during pregnancy is responsible for considerable maternal and foetal morbidity and mortality. Both careful selection of medications and a multidisciplinary approach are required for treating such cases. This study presents a case report of a patient with a known history of generalized myasthenia gravis who presented with preeclampsia at 33 weeks’ gestation. Subsequently, the patient developed recurrent seizures that necessitated the use of multiple medications, including phenytoin, valproic acid, levetiracetam, and propofol. Magnesium sulphate was not administered due to its blocking effect on calcium channels at the neuromuscular junction. The patient underwent a caesarean section under spinal anaesthesia and gave birth to a baby with intrauterine growth restriction (IUGR). Blood pressure control was achieved with the administration of methyldopa and parenteral hydralazine, an increased dose of pyridostigmine, and intravenous immunoglobulin therapy. The status of the patient’s myasthenia gravis remained stable. This case serves to highlight the conflicts in the management of these two disorders and suggests strategies to resolve these conflicts in clinical management.

Keywords: Eclampsia; Myasthenia gravis; Preeclampsia; Pregnancy; Recurrent seizures

Introduction

Myasthenia gravis (MG) is an acquired, organ-specific, autoimmune disease of neuromuscular transmission that is characterized by easy fatigability and skeletal muscle weakness. MG is twice as common among females and often affects them in their 2nd and 3rd decades of life. Preeclampsia is a multi-system disease that is commonly diagnosed by the presence of hypertension and proteinuria during pregnancy; this complication affects 5–8% of all pregnancies and is...
responsible for considerable maternal and foetal morbidity.\textsuperscript{2} Pregnancy and the postpartum period are well-known triggers for an acute exacerbation of symptoms. MG presents a notable challenge throughout pregnancy, especially during labour and the postpartum period. First, there is a risk of a myasthenic crisis associated with the physical and surgical stresses of labour or caesarean section; additionally, pregnancy-related complications, such as pre-eclampsia or eclampsia, may require not only immediate delivery to save the baby and maintain maternal health, but it also introduces the need to control blood pressure, seizures and postpartum pain with limited medication options that do not impair neuromuscular junction transmission. In this case report, the author presents a case of a woman with myasthenia gravis who developed severe preeclampsia with recurrent seizures at 33 weeks’ gestation, discusses the challenges faced in the management of this patient, and provides an overview of the literature concerning the co-occurrence of MG and preeclampsia.

Case report

The patient was a 39-year-old multiparous (G5P4) woman at 33 weeks’ gestation, weighing 89 kg, who was transferred from another centre to the emergency department (ED) of our university hospital with a history of elevated blood pressure for the past two days. Her vital signs in the ED revealed a blood pressure (BP) of 155/100 mmHg, a regular heart rate of 86 beats/min, and a SpO\textsubscript{2} of 100%. Her past medical history was unremarkable, except that she was diagnosed with myasthenia gravis (MG) at age 29 with symptoms that included easy fatigability, bilateral ptosis, diplopia and fluctuating mild weakness of her limbs. Serum acetylcholine receptor antibodies were positive, and a CT of her chest was unremarkable. She had responded well to pyridostigmine 60 mg twice daily at the time of her diagnosis and with a stabilized course of the disease, she weaned herself off medication three years previously. Myasthenic symptoms recurred six months ago at 8—9 weeks’ gestation and she was restarted on pyridostigmine at the previous dose.

On the day of admission, the patient was fully conscious and oriented with bilateral ptosis noted. She demonstrated the power of 4/5 for the proximal muscles and +3 symmetrical deep tendon reflexes in all extremities. The first laboratory assessment revealed unremarkable results [haemoglobin 10.2 mg/dl, platelets 328,000/mm\textsuperscript{3}, serum alanine aminotransferase (ALT): 14 U/L (reference range <34 IU/L), serum aspartate aminotransferase (AST): 31 U/L (reference range <31 IU/L), serum lactate dehydrogenase (LDH): 11 U/L (reference range <234 IU/L), and creatinine 0.8] except that elevated uric acid 8.2 mg/dl (reference range 2.6—6) and proteinuria (100 mg/dl) were noted in routine urinary analysis. An abdominal ultrasound showed a single living foetus in longitudinal cephalic position with an estimated foetal weight of 1610 g and surrounded by adequate liquor. The biophysical profile score was 10. These findings were consistent with IUGR. Baseline spirometry was performed. Her pyridostigmine dose was increased to 60 mg QID, and Methylprednisolone 500 mg BID was started. Initial management was expectant with monitoring of blood pressure and myasthenic symptoms.

On the day after admission, the patient began complaining of a headache, blurred vision and pain in right upper quadrant. Her BP was in a range of 145—155/70—90 mmHg. A 24-h urine collection revealed +3 proteinuria (>8 g). Blood work revealed elevated liver enzymes (ALT: 64 U/L, AST: 138 U/L, LDH: 343 U/L), and a decrease in both the haemoglobin level (7.6 mg/dl) and the platelet count (73,000/ mm\textsuperscript{3}). The results from coagulation studies (i.e., prothrombin time, partial thromboplastin time, and fibrinogen level) were within normal limits. These findings were consistent with severe preeclampsia complicated by HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count). Because she had already received four doses of dexamethasone at another centre (to accelerate foetal lung maturation), the decision was made to expedite delivery by caesarean section.

Before being transported to the operation room (OR), the patient developed generalized tonic-clonic seizures (GTCS) that terminated spontaneously within a minute. Because of the patient’s history of MG, the administration of magnesium sulphate was contraindicated; therefore, she was loaded with intravenous phenytoin (15 mg/kg over 30 min) followed by 100 mg 3 times daily. She was also started on intravenous immunoglobulin therapy (2 g/kg over five days). A caesarean section was performed under regional anaesthesia and resulted in the delivery of a 1480-g baby boy with Apgar scores of 6 and 8 at 1 and 5 min, respectively. In accordance with the Apgar scoring system, the infant’s activity (muscle tone) was given a score of 1 (extremities were flexed) at 1 min and a score of 2 (active motion) at 5 min; the infant’s respiration was slow at 1 min (score of 1) and was followed by a good cry (score of 2) at 5 min. The infant was observed for 72 h in the neonatal intensive care unit for signs of neonatal myasthenia; however, he did not develop any myasthenic symptoms and was later discharged to his mother’s care.

The patient was monitored in the intensive care unit (ICU) with regular BP and oxygen saturation checks. She was fully conscious and oriented and was being closely observed for signs of worsening of myasthenic symptoms and respiratory distress. Postoperative pain was managed with regular administration of paracetamol and ibuprofen; intramuscular lornoxicam 8 mg was available for breakthrough pain. At 3 h post-surgery, the patient developed a second GTCS with a one-minute duration, and her oxygen saturation began to decrease (86%). She was electively intubated, loaded with intravenous valproic acid (2 g over 20 min), and continued on intravenous propofol 25 mg/h for sedation. Despite on being phenytoin and valproic acid, she developed a third GTCS after 3 h of intubation. The dose of propofol was increased gradually to 100 mg/h; she was additionally loaded with Syrup Levetiracetam 1500 mg via the nasogastric tube (NGT), which was followed by a maintenance dose of 500 mg TID. She was started on IV Hydralazine 4 mg/h for high BP (160—170/90—100 mmHg). The patient did not develop any other seizures in next 24 h. The valproic acid was not continued as maintenance because of deranged LFTs. Electroencephalogram was done to rule out non convulsive seizures during the period of sedation. The computed tomography (CT) results were completely normal. She received two units of red blood cells...
during her ICU stay. Propofol was tapered off completely and patient weaned off from mechanical ventilation after 48 hours of controlling seizures. She had no further convulsions. BP was in a range of 125–145/75 to 90 mmHg. There were no further complaints of headache, visual disturbances, or epigastric pain. Her LFT and platelet counts returned to normal values over the next 72 h. Urinary output remained within normal limits throughout the illness. She was kept on Levetiracetam 500 mg TID as a maintenance dose; phenytoin was discontinued. No worsening of myasthenic symptoms was noted during the hospital stay. She completed a five-day IVIG course and continued on pyridostigmine 60 mg QID and Methyldopa 500 mg BID. She was discharged home on day six post-hospital stay. She completed a five-day IVIG course and continued on pyridostigmine 60 mg QID and Methyldopa 500 mg BID. She was discharged home on day six post-

caesarean section and referred to neurology and gynaecology departments for follow-up.

Discussion

Pregnancy has an unpredictable and variable effect on the clinical course of MG. During pregnancy, 30–40% women with MG experience an improvement in their symptoms, 20–30% experience disease exacerbation, and the clinical course remains unchanged for 30–40% of patients.

Preeclampsia complicates 6–8% of all pregnancies and is an important cause of maternal and foetal mortality and morbidity. The team of healthcare professionals caring for the myasthenic mother faces many management challenges, especially during labour and in postpartum period, because precipitation of a myasthenic crisis and late complications of pregnancy may occur. Maternal fatigability may be pronounced, and the mother may get exhausted during the expulsive efforts of the second stage of labour; therefore, the obstetrician should be prepared for an assisted vaginal delivery (vacuum or forceps).

Surgical stress and the use of anaesthetic medications for caesarean sections are additional challenges because both may cause an exacerbation of symptoms. Therefore, caesarean section is not considered a routine mode of delivery for myasthenic patients, and its use is reserved for standard obstetric indications. The use of regional anaesthesia for caesarean sections is preferred for myasthenic patients. Amide local anaesthetics (e.g., lidocaine, mepivacaine, bupivacaine) are recommended, whereas ester local anaesthetics (such as benzocaine, tetracaine, procaine) should be avoided because of the risk of exacerbating the underlying myasthenia. In the present case, the patient was initially quite stable and a vaginal delivery after a delay of 2–3 weeks (at GA 35 weeks) was planned; however, on the day after admission, she developed worsening symptoms of preeclampsia with the first episode of GTCS. Therefore, the decision was made to perform an elective caesarean section under regional anaesthesia (bupivacaine).

The co-occurrence of MG and preeclampsia is rare but dreadfuly problematic from a pharmacologic standpoint. Treating hypertension is a cornerstone of preeclampsia management. The use of beta blockers and calcium channel blockers in these patients should be avoided because of their potential to worsen myasthenic symptoms. Methyldopa and oral hydralazine can be considered to control non-severe hypertension, whereas intravenous hydralazine is the drug of choice to treat severe hypertension (systolic pressure >160 mmHg or diastolic pressure >110 mmHg). In this case, methyldopa was started at admission, and she required intravenous hydralazine for only one day. Both systolic and diastolic blood pressure significantly improved within the first 24 h after delivery. Methyldopa was continued beyond discharge.

Magnesium sulphate is the gold standard therapy for eclampsia and severe preeclampsia because it blocks presynaptic calcium influx at the neuromuscular junction and hence inhibits the excitability of the postsynaptic membrane. However, in myasthenic patients, it results in profound muscular weakness, respiratory failure, and often necessitates mechanical ventilation. Therefore, its use is contraindicated in the management of eclampsia in women with MG. The onset of weakness has been reported to be as early as 10 min after magnesium infusion. Current obstetric guidelines recommend phenytoin as an acceptable method to treat eclampsia in myasthenics, but it can potentially exacerbate myasthenic weakness by reducing the sensitivity of acetylcholine receptors; therefore, it should be reserved to treat refractory seizures. Other acceptable alternative antiepileptic medications for seizure prophylaxis are levetiracetam and valproic acid. Considering hepatotoxic side effect of valproic acid, this should be avoided in patients with deranged liver function. Benzodiazepines (e.g., diazepam, midazolam) can be used for seizure control; however, these medications should be used with caution as they may cause myasthenic weakness and respiratory distress through their muscle relaxant effects via the central potentiation of gamma amino butyric acid (GABA) release. Propofol infusion is most commonly used for sedation of intubated patients in the ICU setting and as an antiepileptic (commonly in the management of status epilepticus). In this case, because of underlying MG, magnesium was never considered despite the patient developing three episodes of GTCSs. In our hospital, phenytoin and valproic acid were available in parenteral forms. Our patient was initially loaded with phenytoin; she was later loaded with valproic acid when she developed a second seizure. Phenytoin was not repeated because of its potential exacerbating effect on myasthenia symptoms; valproic acid was discontinued because the patient developed deranged LFTs and decreased haemoglobin and platelet counts (HELLP syndrome). After intubation, she was continued on propofol infusion for 24 h and loaded with oral levetiracetam via the nasogastric tube, which was followed by a maintenance dose. Propofol was selected over the midazolam due to its rapid onset and short duration of action (half-life 1–2 h), which allowed for rapid titration, early weaning, and extubation after 48 h.

Postoperative pain management in myasthenic patients is also a challenge. In the current scenario, opioid/narcotic analgesics (such as pethidine, tramadol, morphine) are typically used to treat moderate to severe pain. However, in myasthenic patients, the use of these medications should be avoided because they may cause respiration depression. Non-opioid drugs such as acetaminophen and nonsteroidal anti-inflammatory drugs can be used to safely treat
postoperative pain in patients with MG. In our case, postpartum pain was managed very well with regular oral paracetamol and ibuprofen, and intramuscular lornoxicam 8 mg was used for breakthrough moderate to severe pain.

HELLP syndrome usually develops as a complicated form of severe preeclampsia and is associated with an increased risk of maternal and neonatal morbidity and mortality; delivery is the definitive cure for women with HELLP syndrome. Our case was also complicated by HELLP syndrome, which was diagnosed by laboratory evidence suggestive of haemolysis, thrombocytopenia and hepatic dysfunction. The patient required two units of red blood cells for significantly low haemoglobin. At 24 h after delivery, her laboratory parameters began to improve without any other intervention. Renal function and urine output remained within normal limits, and the patient did not develop haematuria.

In patients with MG, the therapeutic regimen during pregnancy should be individualized according to the severity of symptoms, distribution of muscle weakness and the impact of medication side effects on the foetus. Anticholinesterase inhibitors are the drugs of choice for symptomatic treatment of MG. During pregnancy, pyridostigmine (Mestinon®), the most common drug among cholinesterase inhibitors, is considered safe at the recommended dosage of less than 600 mg/day. Intravenous immunoglobulin (IVIG) therapy provides a rapid onset but a temporary (4–10 weeks) improvement in symptoms by interacting with the circulating autoantibodies against acetylcholine receptors; it is indicated in cases of severe disease, in myasthenic crises, and in peripartal management prior to surgery. In this case, the patient’s dose of pyridostigmine was increased from 120 mg/day to 240 mg/day when she was admitted with preeclampsia. Because surgery is considered a stressful condition with the potential to exacerbate myasthenic symptoms and even precipitate crisis, IVIG therapy was started as a part of peripartal management prior to the caesarean section. MG has no effect on the growth and development of the foetus. In our case, foetal growth restriction (IUGR) may have been due to severe preeclampsia.

Conclusions

There is an inherent danger to both the mother and foetus when a pregnant woman with MG develops preeclampsia. Because of the conflict in the management of these high-risk disorders, intensive peripartum monitoring and careful medication selection by the multidisciplinary team of healthcare professionals (neurologist, obstetrician, anaesthetist, and neonatologists) are recommended to avoid exacerbating myasthenic symptoms, to treat preeclampsia related complications (including seizures) and to provide better foetal and neonatal care.

Conflict of interest

The author has no conflict of interest to declare.

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