Combination of myasthenia gravis and HELLP Syndrome in pregnancy: case report and literature review

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Abstract

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. Preeclampsia/HELLP Syndrome is a potentially life-threatening pregnancy complication. The combination of HELLP Syndrome and MG is challenging because the preferred treatment regimens for both conditions generally contradict each other. Our aim is to describe the management options when these two diseases occur simultaneously. We present a case in which a woman with an established diagnosis of MG developed HELLP Syndrome at 31 weeks gestation. Magnesium sulfate prophylaxis was not utilized because of the patient's MG diagnosis. A cesarean delivery was performed. Reported cases with combined diagnoses of MG and preeclampsia/HELLP Syndrome are reviewed and adjustments to treatment plans are discussed. Management of such patients should be done with a multidisciplinary approach in advanced medical centers with careful consideration of the medications used.

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. IgG autoantibodies directed against the postsynaptic nicotinic acetylcholine receptor (AChR) result in skeletal muscle weakness and easy fatigue, with episodic exacerbation and remission. Muscle weakness can be asymmetric, generalized, or involve only a single muscle group. The extraocular muscles are most commonly affected, with resultant diplopia and ptosis. Problems such as laryngeal and pharyngeal muscle weakness, dysarthria, chewing and swallowing difficulties, and inability to clear secretions are the result of bulbar involvement. In severe cases, proximal muscle weakness (neck and shoulder) and involvement of respiratory muscles occur. Characteristically, muscle weakness decreases with rest

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and increases with effort. Infection, stress, surgery, and pregnancy lead to exacerbations in one third of the population.[1] Myasthenia gravis is a rare condition in pregnancy.[2] The incidence of myasthenia gravis among women of reproductive age is 1/10,000-1/50,000.[3] As in many other autoimmune diseases, MG is more common in women than in men.[4] It occurs most frequently in women in their third decade. As far as we know from the information in literature, pregnancy is known to have a variable effect on myasthenia gravis (1/3 stability, 1/3 healing, 1/3 exacerbation). MG exacerbations with pregnancy are most common in the first trimester and the puerperium. Relative immunosuppression in the second and third trimesters results in fewer disease exacerbations during these periods.[5] Pyridostigmine bromide and prednisolone may be used in the treatment of pregnant women with MG. Due to fetal teratogenic effects, immuno-suppressive therapies are not recommended.[6]

Preeclampsia is a pregnancy-specific syndrome that increases the risks of maternal and fetal morbidity and mortality. HELLP (hemolysis, elevated liver enzymes, and low platelet count) Syndrome is a life-threatening condition that sometimes occurs during pregnancy. Although some form of hypertensive disease of pregnancy (preeclampsia, HELLP Syndrome, eclampsia) occurs in approximately 6-8% of all pregnancies, the simultaneous occurrence of preeclampsia or HELLP Syndrome and MG in pregnancy is very rare.[7]

In this article, we describe a pregnant woman with a previous diagnosis of MG who subsequently developed HELLP Syndrome. We also discuss management options with the co-occurrence of these two diseases in pregnancy.

Case report

A 34-year-old nulliparous woman at 31 weeks gestation was admitted to our emergency department due to epigastric pain and severe headache. She had been diagnosed with myasthenia gravis four years previous and had no other comorbid diseases. She stated that she received 60 mg pyridostigmine four times a day and that her MG had remained under control during pregnancy. At the beginning of pregnancy, she had received 40 mg pyridostigmine three times a day. However, dosage and frequency were increased when she was diagnosed with myasthenic crisis demonstrated by the sudden development of breathing difficulty and weakness in the hands and feet in the last two weeks of pregnancy. She stated that she had no other complications during her pregnancy.

On fetal evaluation, a non-stress test (NST) was normal. Ultrasonography revealed a vertex fetus with a normal amniotic fluid index and growth. The patient reported good fetal movement. Pelvic examination showed no cervical dilatation. On physical examination, her blood pressure was 210/140 mmHg. Her hemoglobin level was 14 g/dl and platelet count was 33,000/ml. Her serum aspartate aminotransferase (696 U/l), alanine aminotransferase (370 U/l), and lactate dehydrogenase (501 U/L) levels were high. There was 3+ proteinuria. Total bilirubin, prothrombin time, and partial thromboplastin time were within

normal limits. Neurological examination revealed 4/5 muscle strength in both proximal and distal muscles.

Using findings from a second set of laboratory tests performed two hours later, it was determined that the patient did not have bleeding. However, the patient's hemoglobin level was 11 g/dl, and her platelet level was 31,000/ml. In addition, AST was 750 U/l, ALT was 410 U/l, fibrinogen was 510 mg/dl, indirect bilirubin was 1.3 mg/dl, LDH level was 756 U/L, haptoglobin level was 15 mg/dl, urea was 45 mg/dl, albumin/creatinine was 3.8 mg/dl, and coagulation parameters were observed to be normal. A peripheral spread of the patient was made, and schistocytes were observed. D-dimer levels were found to be normal.

The patient was hospitalized with diagnoses of MG and preeclampsia complicated by HELLP syndrome. The severity of the HELLP syndrome was defined according to the Mississippi Triple Class System. Based on this system, our patient was classified as Class 1 (high) due to high liver enzymes, hemolysis and a thrombocyte count lower than 50.000/ml.

Based on clinical findings of HELLP Syndrome and the second set of laboratory findings, it was decided that urgent cesarean delivery was necessary, primarily because of high AST and ALT levels. In addition, hemoglobin values decreased without any sign of bleeding, there was a decrease in the haptoglobin value, and there was an increase in the indirect bilirubin. The patient was taking medication for myasthenia gravis. Six units of random donor platelets were given to the patient pre-operatively and short-term phenytoin therapy was started.

Magnesium sulfate treatment typically used to treat HELLP Syndrome was not initiated because it increases the chance of crisis in myasthenic patients. However, short-term phenytoin treatment was initiated because it is suggested for the seizure prophylaxis in myasthenic patients who have HELLP Syndrome or who are preeclamptic. Due to her worsening clinical condition, emergency cesarean section was performed under general anesthesia since her platelet count was very low (33,000/ml). A healthy baby boy of 1680 g was born with 1-minute and 5-minute Apgar scores of 8 and 9. The baby was hospitalized in the intensive care unit due to prematurity. Newborn examination revealed no neonatal myasthenia gravis.

Postoperatively, the mother was transferred to the intensive care unit. AST and ALT values gradually returned to normal. In addition, platelet value approached normal. The critical laboratory values of the patient during hospitalization are listed in Table-1. The patient's respiratory parameters were carefully monitored. 70 mg dexamethasone was intravenously administered postoperatively. Because the patient had systolic blood pressure values of 220 to 200 mmHg and diastolic blood pressure values of 140 to 120 mmHg, perlinganit infusion and 250 mg oral methyldopa (2 tablets 4 times per day) were started.

Table 1: Biochemical and hematological data

	Admission	Second day	Third day	Seventh day	Eleventh day
Hb (g/dl)	14	12	8.8	9	8.8
Ht	43	37	28	29	29
Platelet (cells/ml)	33	55	62	79	90
AST (U/l)	696	397	87	35	22
ALT (U/l)	370	306	72	40	29
LDH	501	486	320	280	240

In the postoperative period, 60 mg pyridostigmine was initiated four times a day for the patient. However, when sudden breathing difficulty started 24 hours after the caesarean, it was considered a myasthenic crisis and the dosage of pyridostigmine was increased to 60 mg six times a day. The patient was followed up in the intensive care unit for nine days postoperatively for the possible myasthenic crisis. During the follow-up period, she did not have an MG crisis again and continued to receive methyldopa, pyridostigmine, and dexamethasone.

On postoperative day two, no deteriorations were observed in the clinical findings of the patient. The laboratory findings were as follows; hemoglobin 12 gr/dl, hematocrit 37, platelet 55,000/ml, AST 397 U/l, ALT 306 U/l and LDH 486 U/l. However, on the fifth postoperative day, doxazosin mesylate and valsartan were added to the treatment since blood pressure values had not fallen to normal levels.

On the seventh day in the ICU, the tension values of the patient decreased, and laboratory values were as follows: hemoglobin 9 gr/dl, hematocrit 29, platelets 79,000/ml, AST 35 U/l, ALT 40 U/l and LDH 280 U/l. The patient was discharged from the ICU on the ninth day after her admission to the hospital. The patient was discharged from the hospital on the eleventh day after admission because she had hemoglobin 8.8 gr/dl, hematocrit 29, platelet 90,000/ml, AST 22 U/l, ALT 29 U/l and LDH 240 U/l and tension values were completely normal. Methyldopa 250 mg (2 times per day) and pyridostigmine 40 mg (2 times per day) were prescribed at hospital discharge. At the sixth month postpartum, the patient's blood pressure values were within normal limits and her myasthenia gravis was under control.

Discussion

Coexistence of MG and HELLP/preeclampsia is very rarely seen. There are conflicts in treatment methods in cases with a combination of the two diseases. In other words, the treatment of one disease may worsen the clinical course of the other disease. There are many factors that can trigger a crisis in myasthenic patients. For example, both medical conditions and medications may aggravate MG. These can include pregnancy, thyroid dysfunction, and postpartum use of aminoglycoside, tetracycline, magnesium, β-blockers, and calcium channel blockers. Table 2 represents a detailed list of these factors and medications. When there is a

comorbidity in patients with MG, treatment must be handled with care to assure successful patient management.

Table 2: Factors that can aggravate MG[8]

1.	Pathophysiological
	Stress response: infection, surgery, trauma, pain or emotional stress
	Pregnancy and post-partum
	Temperature: hypothermia or hyperthermia
	Thyroid dysfunction: hypothyroidism or hyperthyroidism
2.	Pharmacological
	Inadequate dosing of anticholinesterase medication
	Antibiotics: aminoglycosides, tetracyclines, others (erythromycin, clindamycin, lincomycin, ciprofloxacin, ampicillin)
	Cardiovascular drugs: β-blockers, calcium-channel blockers, quinine, quinidine, procainamide, lidocaine
	Magnesium
	Anesthetic drugs: volatile agents, neuromuscular blocking agents, local anesthetics
	Others: phenytoin (long-term treatment), gabapentin, lithium, penicillamine, corticosteroids, opioids, iodinated contrast agents, frusemide, thyroxine

When MG and preeclampsia/HELLP Syndrome are seen simultaneously in patients, the most important step in the treatment of preeclampsia is to control hypertension. In normal cases, the first-line choice of drugs is labetalol, with methyldopa and nifedipine as second-line choices. However, labetalol is a beta blocker, and nifedipine is a calcium channel blocker. Both drug groups may exacerbate an MG crisis. Therefore, methylphenidate or hydralazine become the first choices for patients with MG.[9,10] Similarly, magnesium sulfate therapy is the first-line treatment to prevent crisis in preeclamptic patients.[11] However, while magnesium sulfate treatment serves well for the prophylaxis of eclampsia crises, it also causes blockage in the neuromuscular junction in patients with MG and may exacerbate MG symptoms.[12] If patients with MG are treated with magnesium sulfate therapy, it causes dose-dependent side effects such as fatigue, facial twitch, arrhythmia, and muscle weakness. In brief, magnesium sulfate treatment cannot be safely used to avoid eclampsia crises in patients in whom MG and HELLP/preeclampsia coexist. As mentioned previously, release of excessive amounts of magnesium prevents presynaptic acetylcholine release in the neuromuscular junction and avoids postsynaptic stimulation. Instead, short-term phenytoin therapy is recommended for eclampsia prophylaxis in patients with a combination of MG and hypertensive disorders of pregnancy. However, long-term use of phenytoin has the potential of exacerbating myasthenia gravis (Table 2).[13]

Provided that there is no obvious respiratory disorder or bulbar dysfunction in the patient, local anesthesia is preferred for cesarean section in myasthenic patients. Ester local anesthetics are recommended because they might have a longer half-life in patients receiving

anticholinesterase treatment, depending on the inhibition of their plasma cholinesterase.[14] In cases where both diseases coexist, some adaptions in treatment management may be needed as listed in Table 3.

Table 3: Management goals in preeclampsia, usual therapy and modifications in myasthenia gravis[8]

Management goal	Usual treatment	Modifications in myasthenia gravis
Maintenance of appropriate blood pressure		
Non-severe hypertension (systolic pressure140–159 mm Hg and diastolic 90–109 mm Hg)	Most guidelines recommend treatment[9,10] Options: oral labetalol, methyldopa, nifedipine, hydralazine	β-Adrenoceptor blockers and calcium-channel blockers have the potential to exacerbate weakness Consider methyldopa or hydralazine (oral) as first line therapy
Severe hypertension (systolic pressure >160 mm Hg and/or diastolic >110 mm Hg)	Should be treated[15] Options: labetalol (oral/intravenous), nifedipine (oral), hydralazine (intravenous)	Consider hydralazine (intravenous) as first line therapy Use of labetalol (oral/intravenous) described[16]
Seizure prevention and treatment		
Seizure prophylaxis	MgSO4 first line[11]	MgSO4 contraindicated[12,17,18] Consider phenytoin[13] Careful blood pressure control
Eclampsia treatment	MgSO4 first line[11]	Morbidity/mortality benefit of MgSO4 may outweigh risk of myasthenic crisis (especially if prolonged or recurrent seizures) Alternatives (diazepam, phenytoin) are inferior to MgSO4
Prevention of pulmonary edema		
Fluid balance	Cautious management of fluid balance (restrictive fluid therapy if normal renal function present	Cautious management of fluid balance
Safe general anesthesia		
General anesthesia	Blood pressure control Cardiovascular response to laryngoscopy (eg, alfentanil, remifentanil)	Consider intubation without muscle relaxant using alfentanil (up to 50 mg/kg) or remifentanil If muscle relaxant required consider reduced-dose rocuronium with sugammadex reversal

In this article, we presented treatment management in a patient who had a previous diagnosis of MG and developed HELLP syndrome. Magnesium sulphate therapy could not be performed for eclampsia prophylaxis because it was accompanied by MG. The patient was started on short-term phenytoin therapy. Cesarean section was performed due to worsening clinical condition. We wanted to perform spinal anesthesia during surgery; however, general anesthesia had to be performed due to low platelet count. The patient was followed in the intensive care unit after surgery. She was discharged from the hospital on postoperative day 11.

This patient exemplifies the risks posed for mother and child when a pregnant patient has the rare combination of concurrent myasthenia gravis and preeclampsia/HELLP Syndrome. There are conflicts in the management of these diseases. Medication options must be considered for general anesthesia, reduction of hypertension, seizure prophylaxis and other forms of treatment. Local anesthesia is a safer option in many cases.

Previously published case reports have primarily documented patients with a combination of preeclampsia and MG. Only Spiezio et al.7 reported a case with a combination of MG and HELLP. Studies that have been published in PUBMED to date and have reported cases with a combination of MG and preeclampsia are presented in Table 4.

Conclusion

Pregnant women with MG who then develop hypertensive pregnancy complications should be managed in tertiary medical centers capable of providing respiratory support and high-risk obstetric and neonatal care. Patients should be managed by a multidisciplinary team of obstetricians and gynecologists, neurologists, anesthesiologists, and neonatologists. Medications for such patients need to be considered carefully to avoid problematic interactions and unintentional exacerbation of either of the patient's medical conditions.

Table 4: Current myasthenic-preeclampsia/HELLP cases in the literature, MEDLINE search

First Author	Year	Age	G/P	Birth Week	Mode	Medication	Presentation
Cohen BA[12]	1976	37	G3P1	Term	C/S	*Hypertensive treatment: Furosemide, methyldopa *Anticonvulsant treatment: Magnesium sulphate	The patient had a myasthenic crisis due to magnesium sulphate treatment.
Duff GB[19] 1	1979	26	G2P1	37	C/S	*Hypertensive treatment: methyldopa, diazoxide, reserpine, furosemide *Anticonvulsant treatment: Diazepam	The patient was transferred to the ICU (about 16 hours)
Duff GB[19] 2	1979	36	G2P1	36	SVD	*Hypertensive treatment: Ephedrine	Prednisone started in the postpartum period.
Brogan M[20]	1983	37	G1P0	32	C/S	No information	No information
Bashuk RG[21]	1990	19	G1P0	Term	SVD	*Anticonvulsant treatment: Magnesium sulphate	The patient became quadriplegic due to magnesium sulphate treatment. Magnesium sulphate treatment stopped.
Benshushan A[17]	1994	31	G1P0	31	SVD	*Hypertensive treatment: Methyldopa, hydralazine	Postpartum haemorrhage after delivery The patient was transferred to the ICU
Di Spiezio Sardo A[7]	2003	27	G2P0	37	C/S	*Hypertensive treatment: Methyldopa	The patient was diagnosed with severe preeclampsia complicated by HELLP
Hamaoui A[16]	2009	31	G7P3	27	C/S	*Hypertensive treatment: Hydralazine, metoprolol, losartan, amlodipine, labetalol.	HELLP syndrome occurred postpartum third day
Ozcan J[8]	2015	34	G1P0	36	C/S	*Hypertensive treatment: Enalapril	Pyridostigmine and IV immunoglobulin doses were increased in the postpartum period after the operation due to bradycardia
Sikka P[22]	2015	25	G1P0	36	C/S	No information	No information
Lake AJ[23]	2017	28	G3P2	34	C/S	*Hypertensive treatment: Hydralazine, labetalol *Anticonvulsant treatment: Levetiracetam	In the postpartum period, levetiracetam was continued (only 2 days) and hypertension was treated with methyldopa and hydralazine. Clonidine was added on postpartum day 2

G: Gravida, P: Parity, SVD: Spontaneous Vaginal Delivery, C/S: Caesarean Section, ICU: Intensive Care Unit

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