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Chapter

Maternal and Neonatal Outcome of Pregnancies with Autoimmune Myasthenia Gravis

Miljana Z. Jovandaric and Svetlana J. Milenkovic

Abstract

Myasthenia gravis (MG) is an autoimmune neuromuscular disease manifested by the weakness and fatigue in skeletal muscles of the face and extremities. Transient neonatal myasthenia gravis is an uncommon type of MG affecting the newborns with mothers who suffer from the disorder or specific circulating autoantibodies. In most cases, the intensity of transient neonatal MG is not associated with the mothers' condition but rather with maternal antibody titers. The symptoms of transient neonatal MG are hypotonia, feeding difficulties, weak cry, facial diplegia, and breathing difficulties in the affected newborns. The disease is connected to the passive transplacental transfer of anti-acetylcholine receptor antibodies (anti-AChR) or antimuscle-specific tyrosine kinase antibodies (anti-MuSK) from the affected mother to the infant. The postsynaptic neuromuscular junction is damaged by the circulation of autoimmune antibodies, and the antibodies directed against fetal AChR are responsible for the form of fetal onset. Monitoring of these newborns is necessary in the first 7 days upon birth, since during this period of life, TNM symptoms can be detected, especially on the second day. In pregnancy period, myasthenia gravis symptoms may vary and they frequently worsen, sometimes leading to premature delivery.

Keywords: neonates, pregnancy, autoimmune myasthenia gravis

1. Introduction

Myasthenia gravis (MG) is a chronic progressive disease which is manifested in weakness and tiredness of skeletal muscles as most typical symptoms. Neuromuscular transmission defects are responsible for MG onset [1].

The expression "myasthenia gravis" is of Latin origin, where "myasthenia" means "muscle weakness" and "gravis" means "serious" or "heavy." The first report on MG was recorded in 1672 by Thomas Willis (1621–1675), a doctor from England whose main area of research was the nervous system [2].

Although patients suffering from myasthenia gravis do not experience any changes in the nervous and muscular systems, this disease causes a disorder in the transmission of the impulse from the nerve to the muscle, resulting in muscle weakness which is a typical symptom of neurological diseases. One of the most recognizable signals of this disease is the fluctuating weakness in the eyes, bulbar, limbs, and respiratory muscles [3, 4].

MG can be defined as a relatively rare autoimmune disorder, affecting approximately 2 out of every 100,000 people, and can develop at any age. In patients affected by MG, antibodies are formed against acetylcholine nicotinic postsynaptic receptors at the neuromuscular junction of skeletal muscles which leads to progressive skeletal muscle weakness [5]. Myasthenia gravis usually affects female population at the age ranging from 18 to 25, whereas male population is affected by this disease later in life, at the age ranging from 60 to 80 [6].

Depending on the affected skeletal muscle groups, myasthenia gravis is categorized into several classes:

- Class I: Only ocular muscles are weakened with possible weakness of eye closure, while other muscles remain unaffected.
- Class II: Mild weakness of any muscle group is possible as well as ocular muscle weakness of any degree.
- Class IIa: Most commonly causes weakness in limb and axial muscles; occurrence of oropharyngeal muscle weakness is also possible.
- Class IIb: Usually affects either oropharyngeal or respiratory muscles, but it can affect both muscle groups as well; limb and/or axial muscles can also be involved.
- Class III: Mild weakness of any muscle group is possible as well as ocular muscle weakness of any degree.
- Class IIIa: Most commonly causes weakness in limb and axial muscles; occurrence of oropharyngeal muscle weakness is also possible.
- Class IIIb: Usually affects either oropharyngeal or respiratory muscles, but it can affect both muscle groups as well; limb and/or axial muscles can also be involved.
- Class IV: Severe weakness of any muscle group is possible as well as ocular muscle weakness of any degree.
- Class IVa: Most commonly causes weakness in limb and axial muscles; occurrence of oropharyngeal muscle weakness is also possible
- Class IVb: Usually affects either oropharyngeal or respiratory muscles, but it can affect both muscle groups as well; limb and/or axial muscles can also be involved; application of a feeding tube without intubation.
- Class V: Characterized by the necessity of intubation, with or without mechanical ventilation, with the exception of cases of its application in routine postoperative management [7].

2. Myasthenia gravis during pregnancy

Myasthenia gravis can affect the courses of pregnancy and delivery, and it also presents a risk factor for the neonates [8]. On the other hand, pregnancy can

intensify the symptoms of myasthenia which can lead to complications during pregnancy and require a modified treatment. Attention should be paid to ensure an optimal treatment and drug safety before conception. Myasthenia gravis can be transferred to neonates. However, neonatal myasthenia gravis is a treatable and transient disease [9]. MG is relatively frequent in the reproductive period of 1/10,000 to 1/50,000 [10].

The clinical course of MG can be altered unpredictably, and in various ways by pregnancy and the previous pregnancy, experiences are not a reliable source of information on the possible clinical course of subsequent pregnancies [11, 12].

In pregnancy, respiratory function of the lungs is compromised for two reasons. Hypoventilation caused by respiratory muscle weakness, on the one side, and diaphragm elevation caused by fetus growth on the other side lead to the reduction of the lung capacity [13].

MG symptoms can be worsened by puerperal respiratory and urinary tract infections; in order to avoid further complications, a prompt diagnosis and adequate antibiotic treatment of these infections is necessary during pregnancy [14].

It should be taken into consideration that the selected groups of antibiotics—for example, fluoroquinolones (such as moxifloxacin and ciprofloxacin), macrolides (such as azithromycin and erythromycin), and aminoglycosides (such as streptomycin and gentamicin)—can aggravate muscle weakness caused by MG; therefore, these types of antibiotics should be avoided [15].

During pregnancy therapy administration has to be based on individual conditions and symptoms regarding the groups of muscles affected by MG in each patient, bearing in mind the possible side effects and consequences on the fetus [16].

For the symptomatic treatment of myasthenia gravis in the period of pregnancy, acetylcholinesterase inhibitors can be chosen. In most cases of MG during pregnancy, immunosuppressant corticosteroids are effective and hence should be selected in accordance with the symptoms in specific cases of MG [17].

Occurrence of premature membrane rupture and preterm delivery were also reported in cases when patients were treated with high doses of corticosteroids. There are records on temporary increase of MG symptom severity triggered by the introduction of corticosteroid therapy. Although the introduction of immunosuppressive drugs should be avoided before and during pregnancy, therapy reduction or discontinuation bears the risk of triggering a myasthenic crisis or exacerbation in pregnant myasthenic women. In order to control the teratogenic risk to the fetus, immunosuppressive drug dosages have to be carefully balanced and individualized [18].

On the other hand, recent reports suggest that azathioprine (AZA) therapy has shown to be successful in treatments of MG during pregnancy and breastfeeding periods. Even though AZA is absorbed through the placenta, its negative effects on the fetus are relatively minor since the fetal liver is immature and lacks the enzyme responsible for the conversion of AZA into its active metabolites. Cyclosporine A treatment is not considered to be harmful during the period of pregnancy and breastfeeding, but it can also trigger prematurity, spontaneous abortions, and insufficient birth weight at birth. Another drug, mycophenolate mofetil (MMF), is thought to be teratogenic, causing a clinical syndrome which includes hypoplastic nails, shortened fifth fingers, oral cleft, microtia, diaphragmatic hernia, and micrognathia [19].

MG rarely affects the first stage of delivery, mostly because in this stage smooth muscles are involved. However, in the second stage, the mother can experience fatigue due to the involvement the voluntary striated muscles [20].

In this stage of delivery, mothers frequently feel exhausted, which may involve myasthenic crisis; therefore, the obstetrician needs to be ready for an assisted vaginal delivery if required (e.g., performing vacuum extraction or using forceps) [21].

Since MG patients are particularly sensitive to a number of anesthetics, an anesthesiologist should be consulted at the beginning of the pregnancy. Both in vaginal and in surgical deliveries, epidural anesthesia not exceeding the tenth thoracic vertebra level is advisable in order to ensure an adequate analgesia. While amide-type local anesthetic agents (such as lidocaine, mepivacaine, and bupivacaine) have no impact on myasthenia, ester-type drugs (e.g., benzocaine, tetracaine, and procaine) are not the drug of choice because of the risk of aggravation of the existing myasthenia. Nonsteroidal anti-inflammatory medications (e.g., ketorolac tromethamine) and paracetamol (acetaminophen) may be included to ease postpartum or postoperative pain, while narcotic analgesic agents that can contribute to respiratory depression are to be avoided [22].

Although anti-acetylcholine therapy can be used safely by nursing mothers suffering from MG, it may exacerbate symptoms of transient *neonatal myasthenia gravis* (TNMG), since anti-acetylcholine receptor antibodies (AChR-Ab) are contained in breast milk [23, 24].

Glucocorticoids and AZA are also not contraindicated in myasthenic mothers, but a liver function test must be performed, and complete blood count must be monitored in the newborns breastfed by myasthenic mothers. However, in breastfeeding mothers with MG, mycophenolate mofetil is contraindicated [23].

Taking care of the newborn can be particularly strenuous for myasthenic mothers due to the lack of sleep at night and constant daily caring for the infant. These extreme efforts may worsen the clinical symptoms of MG. In cases where immunosuppressive therapy has to be initiated or restarted after giving birth, contraceptive counseling is strongly recommended. A carefully chosen contraceptive has to be prescribed a minimum of 1 month prior to the initiation of immunosuppressive therapy, and it should not be discontinued 6 months prior to a new pregnancy. A cyclic withdrawal of oral contraceptives has been reported to initiate worsening of MG symptoms. In such cases, continuous hormonal contraception or an intrauterine device is more preferable [25].

3. Newborns by myasthenic mothers

Neonatal MG is typically triggered by an autoactivation of the immune system. The causative factor is not known, but the disorder may have a genetic defect, leading to congenital MG, or placental transmission of maternal antibodies, resulting in transient neonatal MG. TNM is a temporary condition caused by transplacental circulation of mothers' antibodies. It develops in 10–20% cases of infants with myasthenic mothers, due to transplacental circulation of mothers' antibodies [26, 27].

In these infants general muscle weakness is noticeable together with deficient suck, lethargy, and breathing difficulty until the fourth day upon birth. These symptoms are considered to be the consequence of transplacental transfer of antibodies. However, this causative effect is somewhat unclear, since a close correlation has neither been found between the severity of MG in mothers and existence of neonatal myasthenia nor between neonatal myasthenia gravis and maternal anti-AChR antibody titers. The correlation might be explained by the protective role of alpha-fetoprotein in neonatal myasthenia gravis, as alpha-fetoprotein has been proven to inhibit the binding of myasthenia gravis antibody to its receptor [28, 29].

Premature delivery occurs in approximately 35% of cases of mothers. The most common fetal abnormalities are pulmonary hypoplasia and arthrogryposis. Death from malformations attributable to myasthenia gravis has also been reported [30].

Although TNMG can potentially be a life-threatening condition, it can have excellent prognosis if it is timely identified and properly treated [31].

Transient neonatal myasthenia gravis (TNMG) is a rare form of MG which affects the infants whose mothers have the disorder or specific circulating autoantibodies [32].

There are cases in which the mother is asymptomatic. The level of severity is not necessarily connected with the mother's condition but rather with maternal antibody titers. The onset is typically shown immediately after birth. The recognizable symptoms in infants affected by TNMG are hypotonia, feeding difficulties, weak cry, facial diplegia, and respiratory distress in the affected neonates. Most commonly, these symptoms recede gradually with the decrease in maternally derived antibodies. The risk of this disorder continues for the subsequent births. The exact risk factors for the condition are yet to be identified. If treated promptly, the symptoms resolve within 2 months upon birth [33, 34].

TNMG is connected to the passive transplacental transfer of anti-acetylcholine receptor antibodies (anti-AChR) or anti-muscle-specific tyrosine kinase antibodies (anti-MuSK) from the affected mother to the infant. The postsynaptic neuromuscular junction is damaged by the circulation of autoimmune antibodies, and the antibodies directed against fetal AChR are responsible for the form of fetal onset [35].

The pathogenic role of acetylcholine receptor (AChR) antibodies has not been precisely determined. Despite the fact that passive-transfer acetylcholine receptor (AChR) antibodies are identified in most of these neonates, only a small percentage of infants develop the symptoms. A biological marker for prenatal detection of this group of neonates has not been identified yet, but recent reports suggest that HLA typing can be used successfully for this purpose. Final diagnosis can be given when the therapy of acetylcholinesterase agents temporarily improves the neuromuscular transmission disorder. Serum AChR antibody titers behave in the same way as the maternal pattern.

Anticholinesterase agents and supportive management before breastfeeding are required in approximately 80% of cases. The symptoms disappear spontaneously in most cases [27, 36, 37].

4. Conclusion

Newborns of mothers with MG manifest clinical features of TNM relative to the phase of the mothers' disease and transplacental transfer of antibodies to acetylcholine receptors throughout the placenta. These newborns need to be monitored until their seventh day of life, as TNM symptoms can be visible from birth to 7 days of life, though most commonly on the second day of life. The clinical course of myasthenia gravis during pregnancy is variable, with a significant proportion of patients experiencing worsening of clinical symptoms and premature delivery.

Conflict of interest

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Author details

Miljana Z. Jovandaric* and Svetlana J. Milenkovic
Department of Neonatology, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

*Address all correspondence to: rrebecca080@gmail.com

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