sciendo
ПРИЛОЗИ. Одд. за мед. науки, XLIV 2, 2023 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLIV 2, 2023 MASA

10.2478/prilozi-2023-0036 ISSN 1857-9345

TRANSIENT NEONATAL MYASTHENIA GRAVIS: A CASE REPORT

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ABSTRACT

Transient neonatal myasthenia gravis (TNMG) is a neuromuscular disorder that occurs in infants born from mothers with myasthenia gravis (MG) due to transplacental transfer of antibodies against the acetylcholine receptor. TNMG is a rare form occurring in 10-15% of infants born from mothers with MG.

We present a case of a newborn with TNMG with generalized hypotonia and respiratory distress. The newborn shows symptoms of hypotonia, weakened reflexes, poor crying, difficult sucking and potentiated tachydyspnea after 24 hours of birth and needs of assisted mechanical ventilation. Based on the mother's positive history of MG and the high titer of mother's (8.43nmol/l) and newborn's (9.088nmol/l) anti-AChR antibodies, TNMG was diagnosed. The baby was treated with assisted mechanical ventilation and neostigmine until the anti-AChR antibody titer was negative. Adequate management of the newborn resulted in a positive outcome and evident withdrawal of the symptoms.

Although TNMG is one of the rare neuromuscular disorders in newborns that can be treated, a multidisciplinary approach in the management of pregnant women with MG and newborns through timely diagnosis and early appropriate treatment, results in successful resolution of this condition.

Keywords: transient neonatal myasthenia gravis, neostigmine, myasthenia gravis, hypotonia

INTRODUCTION

Transient neonatal myasthenia gravis (TNMG) is a disorder in infants born from mothers with myasthenia gravis (MG), due to transplacental transfer of maternal antibodies against acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) [1,2].

Myasthenia gravis is an autoimmune disorder where autoantibodies target the postsynaptic membrane of the neuromuscular junction, causing skeletal muscle weakness and fatigue. In more than 90% of patients, the antibodies are against the muscle acetychoin receptor (AChR), and a small proportion of patients have antibodies against the muscle-specific tyrosine kinase (MuSK) or liporptein receptor-related protein 4 (LPR4) [3]. MG is a relatively rare disorder with an incidence of 1.7-30 cases per million people per year and a prevalence of 77.7 cases per million people [4.5], with a female predominance of 18-25 years of age [6]. MG was first studied and noted in the literature in 1672 by the English doctor Thomas Willis [7].

Several variants of MG are distinguished in the pediatric population: congenital MG, which is a rare autosomal recessive genetic disorder, transient neonatal MG, which is characteristic of newborns born from mothers with MG, and juvenile MG, which is most common in childhood and is identical to adult autoimmune MG.

TNMG is a rare form occurring in 10-15% of newborns born from mothers with MG (8). This

is a potentially life-threatening condition if it is not identified in time and treated appropriately (9). First symptoms in newborns with TNMG occur within 3-72 hours after birth (10). Dominant signs and symptoms in these newborns are: generalized hypotonia, weakened or absent primitive reflexes with preserved deep tendon reflexes, difficult sucking, poor crying, respiratory muscle weakness accompanied by respiratory distress, apnea and infections. Other symptoms in these patients are diplegia or facial paresis (37-60%), swallowing and sucking difficulties (50-71%), ptosis (15%) and ophthalmoparesis (8%) [11-13].

In this article, we present a case of a newborn with TNMG from a mother with MG with respiratory distress and potentiated hypotonia requiring assisted mechanical ventilation and pharmacological therapy.

CASE REPORT

The presented case refers to the first child of a 29-year-old mother with a generalized form of MG (MGFA IIb) who had thymectomy 2 years before pregnancy. During the pregnancy, she was in a relatively stable condition, on therapy with pyridostigmine and prednisolone. A male baby was born at 38 weeks of gestation by caesarean section, with a cephalic presentation and a birth weight of 3,200 grams, with Apgar score of 8/8. The first physical examination of the newborn showed mild hypotonia, weakened primitive reflexes and poor crying. Initially, the newborn was in the neonatal transient care unit, but due to the manifested hypotonia, poor crying and moderate dyspnea after 24 hours of birth, he was transferred to the Neonatal Intensive Care Unit (NICU). Oxygen therapy with a hood (3l/min.) and double antibiotic therapy were started. After 2 hours, irregular breathing and tachydyspnea were noted in the newborn. A non-invasive ventilation with CPAP (FiO2=30%) was initiated. Respiratory distress was accentuated, with reaspirated acidosis and hyposaturation in gas analyses, accompanied by generalized hypotonia. After 1 hour the infant was intubated and connected to invasive mechanical ventilation-SIPPV+VG (FiO2=35%). Blood for anti-AChR antibodies was taken, and neostigmine therapy was started.

According to the high titer of anti-AChR antibodies=9.088nmol/l (positive≥0.5nmol/l), clinical presentation of the infant and the history of the mother's disease, the diagnosis of TNMG was confirmed.

After the neostigmine therapy, the respiratory function was stabilized, gas exchange and tonus improved, and weaning was started from mechanical ventilation. The newborn was extubated the second postnatal day. In the next 48 hours, he was relatively stable, after which he again developed severe dyspnea, respiratory acidosis and hypotonia, followed by elevated inflammatory markers and leukopenia (CRP=36mg/l, Le=3.2x109/l). He was intubated again and connected to mechanical ventilation - SIPPV+VG. The antibiotic therapy was changed (cefepime+meropenem).

During the next 3 days, the newborn needed respiratory support, with a gradual change of mechanical ventilation modes (SIPPV+VG/PSV+VG/CPAP-NIV) until complete extubation, with stable respiratory function and proper blood gas analyses.

Due to the generalized hypotonia and the weak sucking and swallowing reflex, nutrition with adapted milk formula was started with an orogastric tube. After the stabilization of the respiratory function, improvement of tone and reflexes, the feeding was continued through a bottle with a pacifier.

The control titer of anti-AChR antibodies (5.17 nmol/l) were decreased in the following 14 days, and the clinical condition of the newborn was improved, but the neostigmine therapy was still continued.

There was a normal ultrasonographic screening of the heart, urogenital tract and CNS in the newborn.

Due to the complex clinical condition and need for neostigmine therapy, until the titer of anti-AChR antibodies became negative and the need for intensive monitoring, the newborn was hospitalized in NICU all time. He got discharged from hospital at the age of 56 days with stable vital parameters, good tone and reflexes.

DISCUSSION

TNMG is relatively benign and rare neuromuscular disorders that is treatable in newborns. 75-80% of mothers with MG have anti-AChR antibodies. Therefore, TNMG caused by this type

of antibodies is the most common form. AChR antibodies belong to subclasses IgG1 and IgG3, which bind to the extracellular domain of the receptor, activate the complement cascade, causing an inflammatory reaction with cytokines, which leads to disruption of signal transduction at the postsynaptic membrane. Anti-MuSK antibodies belong to the IgG4 subclass and, unlike anti-AChR antibodies are unable to independently activate complement and bind to Fc receptors and are less effective in inducing antigenic modulation. Also, the risk of TNMG mediated by anti-MuSK antibodies may be lower than that of anti-AChR antibodies, because active transport of IgG across the placenta favors IgG1 over IgG4.

Antibodies provoke the disease by acting on the receptors by: accelerating the degradation of the receptors, blocking the access of acetylcholine to the AChR, and activating and amplifying the complement system, promoting the destruction of the postsynaptic membrane [3]. The presented case of TNMG is mediated by anti-AChR antibodies, which was demonstrated by the high titer of anti-AChR antibodies in a newborn from a mother with MG.

Two forms of TNMG are clinically distinguished: typical (71%) and atypical (29%). The atypical is also a severe form, which is manifested by arthrogryposis multiplex congenita, pulmonary hypoplasia and fetal or neonatal death [12,14]. The typical form includes the symptoms of generalized hypotonia, weakened or absent primitive reflexes, but preserved deep tendon reflexes, difficult sucking, poor crying, respiratory muscle weakness accompanied by respiratory distress. Our case belongs to the typical form of TNMG, where generalized hypotension dominates and potentiated weakness of the respiratory muscles, which, in addition to pharmacotherapy, also required assisted mechanical ventilation.

The diagnostic tools for TNMG include a positive family history for a mother with MG, anti-AChR antibody titer testing in the suspected infant, the neostigmine test, and an electromyogram test (EMG test). A positive anti-AChR antibody titer confirms the diagnosis, and additional further investigations are performed only when the clinical condition is unclear.

The diagnostic evaluation of a hypotonic newborn is always a challenge, and this condition should be differentiated from spinal muscular atrophy, neonatal sepsis, infantile botulism, congenital muscular dystrophies, mitochondrial myopathy, anomalies of the central nervous system, Mobius syndrome, and others [10,15].

The individual treatment of newborns with TNMG includes supportive therapy of the vital functions, respiratory system and nutritional needs, as well as pharmacotherapy. The use of anti-cholinergic drugs such as neostigmine (0.04 mg/kg i.m or s.c. every 4-6h) or pyridostigmine is recommended for the treatment of TNMG. Due to the risk of arrhythmia, intravenous administration of neostigmine is not recommended in children under two years of age [16]. Immunomodulatory and immunosuppressive therapy used in adults with MG is not recommended for newborns. Certain antibiotics (aminoglycosides, fluoroquinolones, chloroquine, macrolides) can potentiate the myasthenic crisis in the newborn and should be avoided [17,18]. In our case, we associate the use of the aminoglycoside antibiotic and the infection with the second respiratory crisis and the need for mechanical ventilation, which indirectly confirms the fact of potentiation of the myasthenic crisis and improvement of the newborn's condition after changing the antibiotic.

IVIG, although used in adults with MG, has not been shown to be beneficial in TNMG [19,20]. Plasmapheresis is effective in reducing circulating anti-AChR antibodies in adults with MG. In TNMG, exsanguinous transfusion instead of plasmapheresis could be useful, but there are still divided views about the use of this treatment in newborns. Neonatal Fc receptor antagonists (FcRn inhibitor) are under research as a new treatment for this condition, which improves IgG catabolism leading to a reduction in the concentrations of pathogenic autoantibodies [3].

About 10% of newborns died from TNMG in the past due to late and inadequate therapy [21]. Today, complete remission of TNMG is expected in 90% of newborns in less than 2 months, and in 10% in 4 months [11,14,22]. The risk of a newborn with TNMG in the next pregnancy is significantly higher and the recurrence rate increases to 75% [3]. There is no gender or racial predominance, and no definite association between the severity of the disease in the mother and the clinical condition of the newborn. No biological marker has been identified for prenatal diagnosis in these newborns yet, and the relationship between TNMG and HLA typing is still controversial [3].

CONCLUSIONS

TNMG is a rare disease in infants born from mothers with MG. This condition in the neonatal population is manifested from asymptomatic to a severe clinical condition of generalized hypotonia and severe respiratory distress, which, if not properly treated in time can be fatal. Severe respiratory distress requiring assisted mechanical ventilation occurs in 29% of cases [11,12,23]. The presented case refers to a newborn with TNMG, which is a rare form that required invasive mechanical ventilation and pharmacotherapy, with timely and successful treatment.

A positive family history, the clinical presentation in the newborn and a high titer of anti-AChR or anti-MuSK antibodies in the newborn clearly indicate TNMG. These infants have no risk of developing MG over the course of life. A modern multidisciplinary approach in the management of pregnant women with MG and their newborns is essential to properly address this condition.

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Резиме

ТРАНЗИТОРНА НЕОНАТАЛНА МИЈАСТЕНИЈА ГРАВИС: ПРИКАЗ НА СЛУЧАЈ

Сања Ристовска, Орхидеја Стомнароска, Рената Димитриоска

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Транзиторната неонатална мијастенија гравис (ТНМГ) е невромускулно нарушување што настанува кај новороденчења родени од мајки со мијастенија гравис (МГ), поради трансплацентарен пренос на антитела против ацетилхолинскиот рецептор. ТНМГ е ретка форма што се јавува кај 10–15 % од новороденчињата родени од мајки со МГ.

Во овој труд се презентира случај на новороденче со ТНМГ со генерализирана хипотонија и респираторен дистрес. Новороденчето пројавува симптоми на хипотонија, ослабени рефлекси, слаб плач, отежнато цицање и потенцирана тахидиспнеа по 24 часа од раѓањето, по што има потреба од асистирана механичка вентилација. Врз основа на позитивната анамнеза од мајката за МГ и високиот титар на anti-AChR antiela кај мајката (8,43 nmol/l) и кај новороденчето (9,088 nmol/l), дијагностицирана е ТНМГ. Третманот вклучуваше потреба од асистирана механичка вентилација и неостигмин сè до негативизирање на титарот на anti-AChR antiela. Соодветниот менаџмент на новороденчето резултираше со позитивен исход и евидентно повлекување на симптомите.

ТНМГ, иако е едно од ретките невромускулни нарушувања кај новроденчињата што се лекува, сепак, мултидисциплинарниот пристап во водењето на бремените жени со МГ и новороденчињата преку навремената дијагноза и ран соодветен третман, резултира со успешно решавање на оваа состојба.

Клучни зборови: транзиторна неонатална мијастенија гравис, неостигмин, мијастенија гравис, хипотонија