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Case Report

The expectant management of a rare neonatal disease: transient neonatal myasthenia gravis

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ABSTRACT

Background. Transient neonatal myasthenia gravis (TNMG) is an acquired disease which occurs in 10 to 20% of infants born to a mother with myasthenia gravis. Even though it is a self-limiting disorder, it may potentially be life-threatening if prompt diagnosis is not made, and expedient supportive respiratory management is not initiated when required.

Case. Here we describe three infants with TNMG. Two of them developed symptoms of TNMG within 24 hours of life, but one developed symptoms at 43 hours of life. One of the patients had an atypical form of TNMG with contracture and hypotonia. The other two infants survived a typical form of TNMG with hypotonia and poor sucking. All cases resolved spontaneously by one to two weeks of life with conservative management.

Conclusions. Infants born to mothers with myasthenia gravis need to be monitored closely for symptoms of TNMG for the first 48 to 72 hours of life. However, the majority of infants with TNMG traverse a benign course and resolve spontaneously with expectant care.

Key words: transient, neonatal myasthenia gravis, acetylcholine receptor antibodies.

Transient neonatal myasthenia gravis (TNMG) is an acquired disease which occurs in 10 to 20% of infants born to a mother with myasthenia gravis.[1-3] Transient neonatal myasthenia gravis occurs as a result of the passive transfer of maternal antibodies affecting the fetus' synaptic transmission at the motor end plate. It is characterized by abnormal muscle fatigability. Even though a normally self-limited disorder, TNMG may be potentially life-threatening if this condition is not recognized when prompt supportive respiratory management may be required.

Here we describe three infants with TNMG. Two of them developed symptoms of TNMG within 24 hours of life, but one developed symptoms at 43 hours of life. One of the patients had an atypical form of TNMG with contractures and hypotonia. In contrast, the other two infants survived a typical form of TNMG, with hypotonia and poor sucking. All cases resolved spontaneously within one to two weeks of life with conservative management. Informed consents were obtained from the respective families for the photos and write-up about these cases.

Case Report

Case 1 was a baby girl who was born at 39 weeks of gestation via spontaneous vertex delivery. She was noted to be small for gestational age, with a birth weight of 2320 grams. She was the second child born to a 25-year-old mother diagnosed with myasthenia gravis (MG) diagnosed at the age of 23, eight months after delivering her first child, when she presented with ptosis and difficulty in swallowing.

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The mother's blood for was positive acetylcholine receptor antibody. She had developed three episodes of myasthenia crisis two months before she conceived this baby and was on oral pyridostigmine 60 mg four times daily and oral azathioprine 125 mg daily. She was offered a thymectomy, which was postponed because of the pregnancy. Otherwise, there was no history of polyhydramnios during pregnancy.

Although this baby was vigorous at birth, she was noted to have poor sucking and a weak cry shortly after. Examination revealed facial diplegia (Fig. 1), poor sucking, and hypotonia of all four limbs with fixed flexion deformity involving both elbows (Fig. 2) and knees. A diagnosis of TNMG was made, and her blood investigation later showed that acetylcholine receptor (AChR) antibodies were 30-fold above normal (8.4 nmol/L [Normal level: < 0.25 nmol/L]).

Given her symptoms and maternal intrapartum history of prolonged rupture of membranes which occurred 24 hours prior to delivery, she was treated for presumed sepsis with intravenous penicillin and gentamicin. She subsequently required respiratory support due to recurrent apnoea, which resolved after stopping the aminoglycoside. She was on tube feeding for two weeks as her sucking was poor. Her symptoms improved gradually after the second week of life with good sucking and improved muscle tone. She was started on physiotherapy for her contracture during her stay in the ward. She was discharged well, and on subsequent follow-up visits the contractures at both elbows and knees were less severe.

Case 2 is the younger sibling of Case 1, and was born one year later via elective Caesarean section at 38 weeks. Throughout the pregnancy, her mother was in a remission state while on oral prednisolone 15 mg and oral azathioprine 125 mg daily. She was born small for gestational age, birth weight of 2470 gr. She developed respiratory distress shortly after birth, requiring non-invasive ventilation for seven hours and was subsequently stable on room air. At 30 hours of life, she developed bilateral ptosis, poor sucking, hypotonia (Fig. 3) and a weak cry. Blood investigation also showed elevated AChR antibodies, 13-fold above normal (3.45

Fig. 1. Case 1 with facial diplegia, hypotonia and had poor sucking.

Fig. 2. Case 1 showing fixed flexion deformity of both elbows.

Fig. 3. Case 2 with bilateral ptosis, facial diplegia, hypotonia and poor sucking.

nmol/L [Normal level: < 0.25 nmol/L]). Despite a lower antibody level, this younger sibling's presentation was more acute. She was tube fed for the first four days of life. Sucking improved subsequently with normal muscle tone. She was discharged earlier than her older sibling, on day six of life.

Case 3 was a baby girl born via elective Caesarean section at 38 weeks. She was the second child to a mother aged 35 with ocular myasthenia gravis, diagnosed at 28 years of age. The mother had been on oral pyridostigmine 60 mg four times daily throughout pregnancy and remained in remission. This baby was also vigorous at birth, like the previous two cases, but developed respiratory distress soon after in the postnatal ward at 43 hours of life. Upon examination, she was noted to have poor sucking and hypotonia. She was on respiratory support with a high-flow nasal cannula for one day. Blood investigation showed elevated AChR antibodies, 30-fold above normal (8.5 nmol/L [Normal level: < 0.25 nmol/L]). She received syringe feeding for three days until her sucking had improved. She was discharged well on day five of life.

Discussion

The prevalence of MG occurring in the general population is 77.7 cases per million persons.[4] The infant born to a mother with MG is at risk of having TNMG with an incidence of 10 to 20%.[1-3] However, the risk of TNMG in a sibling, is significantly higher in subsequent pregnancies, as described in our cases.[2]

Infants born to women with MG may have a transient neonatal myasthenic syndrome because of placentally transferred maternal anti-AChR or anti-muscle-specific receptor tyrosine kinase (MuSKR) antibodies.[5] Circulating maternal autoimmune antibodies in fetal circulation are thought to block the postsynaptic neuromuscular junction.[6] The pathogenic role of these antibodies is still unclear because there was no correlation between maternal disease severity or maternal antibody titres with neonatal myasthenia. However, specificity of antibodies, in that, a higher ratio of anti-fetal to anti-adult AChR antibodies in the myasthenic mother may predispose to the occurrence of neonatal MG, and more severe or persistent myopathic features such as, arthrogryposis.[3]

There are two clinical forms of TNMG: the typical presentation, which is more common, with an incidence rate of approximately 71% and, the atypical form in about a third (29%).[1] The typical form commonly develops symptoms more rapidly, as in Case 2 and 3, that include poor sucking and swallowing, weak cry, facial diplegia and ptosis, ophthalmoparesis, generalized hypotonia and respiratory distress. Some infants develop severe respiratory distress requiring assisted mechanical ventilation. In a systematic review by Kochhar et al.[7], only one out of 147 patients required intubation. In two-

thirds of infants, symptoms develop within the first few hours after birth, while most infants (78%) would have developed symptoms by the first 24 hours of life. Cases presenting with symptoms beyond 72 hours of life are extremely rare.[1]

In contrast, the atypical form of TNMG, such as Case 1, may present with clinical features that include multiple joint contractures and arthrogryposis, which gradually improve with time. It may also be associated with pulmonary hypoplasia, likely attributed to impaired chest wall development or reduced fetal breathing efforts.[8] Fetal or early neonatal death is more common in this form.[1,5,9] The risk of this condition continues for subsequent births.[8]

The presence of high concentrations of anti-AChR or anti-MuSKR antibodies in the plasma of affected newborns, along with the maternal clinical history of MG, is pathognomonic of TNMG.[5] Other investigations for TNMG, but less commonly employed, include pharmacologic testing with the administration of acetylcholinesterase agents (e.g., neostigmine methylsulfate or edrophonium chloride) which transiently correct the neuromuscular transmission defect. Repetitive nerve stimulation is rarely done as a test.[1]

Certain drugs, such as aminoglycoside, may potentiate myasthenia and, therefore, should be avoided. The worsening of symptoms is probably due to this drug competitively inhibiting the release of acetylcholine from the presynaptic membrane.[10]

All three patients recovered over the first or two weeks of life. An affected infant would regain normal muscle strength after the circulating maternal antibodies disappear from the body. Complete recovery is expected in less than two months in 90% of infants, and the remaining 10% should fully recover by four months of age without residual neurological impairment, especially in the typical form.[1]

In patients with mild symptoms, giving frequent small oral feedings and continuous close monitoring during the first week of life is recommended before it is safe to discharge. For patients with moderate to severe symptoms, and to accelerate success in oral feeding, neostigmine methylsulfate may be an option but is rarely sought after. Neostigmine is administered intramuscularly or subcutaneously (0.05 mg/kg) or orally (0.5 mg/kg), up to a half-hour before feeding.[1] However, neostigmine administration may cause adverse side effects such as respiratory depression, cardiac arrhythmia and gastrointestinal disturbance. These side effects may be difficult to distinguish in a neonate. In the majority of infants, the condition resolves spontaneously.[11] Without pharmacological intervention, symptoms will gradually resolve in one to four weeks.[12]

Although plasmapheresis, intravenous immunoglobulin (IVIG), and corticosteroids are all efficacious in treating MG in older children and adults, these are rarely needed and only necessary for the management of severely affected neonates for rapid removal of circulating antibodies in life-threatening situations.[2] Our cases did not need IVIG as they were mild, transient and the potentially life-threatening respiratory depression was promptly recognised and ameliorated with non-invasive ventilatory support. IVIG is a high-cost drug with immune-modulating effects that may potentially pose long-term side effects on the developing immune system. Also, the usage of IVIG in treating TNMG has variable outcomes, and future studies on IVIG and exchange transfusion in severe TNMG are needed.[13-15]

As a conclusion, an infant born to a mother with MG needs to be observed for symptoms of TNMG at least over the first 48 to 72 hours of life, regardless of the severity of maternal MG status. However, as in the presented cases, it is emphasised that most infants with TNMG resolve spontaneously with expectant care.

The atypical form of TNMG may be more serious, affecting the limb musculature and possibly lung development. These infants are at risk of intrauterine or early neonatal death.

Ethical approval

Informed consent was obtained from the family for the purpose of writing this case report for publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: FM; data collection: SI; draft manuscript preparation: FM, SI, FCC. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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