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Myasthenia Gravis with Anti-Muscle-Specific Tyrosine Kinase Antibody during Pregnancy and Risk of Neonatal Myasthenia Gravis: A Case Report and Review of the Literature

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Keywords
Myasthenia gravis · Anti-muscle-specific tyrosine kinase antibody · Pregnancy · Transient neonatal myasthenia gravis

Abstract
A 31-year-old woman presented with a nasal voice, dysarthria, and upper limb weakness during her first pregnancy. Soon after delivery of her first baby, her symptoms disappeared. At the age of 34 years, during her second pregnancy, her nasal voice re-appeared. After delivery of the second baby, her nasal voice worsened, and bilateral eyelid ptosis and easy fatigability were also evident. She was referred to our hospital. Because of her myasthenic symptoms and anti-muscle-specific tyrosine kinase (MuSK) antibody (Ab)-positive status, she was diagnosed as having myasthenia gravis (MG). Her symptoms were worse than those in her first pregnancy. She was treated with oral steroid and double filtration plasmapheresis. After initiation of treatment, her myasthenic symptoms improved completely. In addition, her baby developed

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transient neonatal MG (TNMG) on the fourth day after birth and then gradually recovered over 30 days. It should be noted that symptoms of patients with anti-MuSK Ab-positive MG (MuSK-MG) can deteriorate during pregnancy, and the babies delivered of patients with MuSK-MG have a high probability of developing TNMG.

Introduction

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction. MG is clinically characterized by weakness and fatigue of the skeletal muscles [1]. Approximately 80% of patients with MG are positive for anti-acetylcholine receptor (AChR) antibody (Ab), whereas about 5–10% are positive for anti-anti-muscle-specific tyrosine kinase (MuSK) Ab [2–4]. MG tends to occur in young women (aged <40 years) [1]. Therefore, since this corresponds to the age of pregnancy and childbirth, safe treatment of their MG is needed. In general, there is a 40% chance of exacerbation of MG during pregnancy and an additional 30% risk in the puerperal period [5]. On the other hand, pregnancy in patients with anti-MuSK Ab-positive MG (MuSK-MG) has rarely been reported [2–4, 6–10], and the association between MG and pregnancy has not been clarified. The case of a patient with MuSK-MG whose symptoms repeatedly worsened during pregnancy is presented.

Case Report

Mother

A 31-year-old woman became pregnant for the first time. In the twentieth week of her pregnancy, she developed dysarthria with a nasal voice for 2 weeks. At 28 weeks of pregnancy, she was not able to lift heavy objects because of bilateral upper limb proximal fatigable weakness. After delivery of her first baby, her symptoms improved. At the age of 34 years, she became pregnant with her second baby. At 12 weeks of pregnancy, she again developed dysarthria with a nasal voice. After caesarean section (CS) delivery at 37 weeks of pregnancy, her nasal voice deteriorated, and bilateral eyelid ptosis and easy fatigability were also evident 2 weeks after the delivery. She was referred to our hospital for neurological evaluation 3 weeks after delivery. She had bilateral eyelid ptosis and double vision due to bilateral abduction limitation. She had a nasal voice. Her muscle strength of the neck and proximal upper limbs were weakened, with diurnal fluctuation. Her blood tests including complete blood count, biochemical tests, and thyroid function were within normal limits. Anti-nuclear Ab, anti-ribonucleoprotein Ab, anti-SS-A Ab, anti-SS-B Ab, proteinase 3-anti-neutrophil cytoplasmic Ab (ANCA), and myeloperoxidase-ANCA were negative. The anti-AChR Ab level was 0.4 nmol/L (normal range, <0.2 nmol/L), and the anti-MuSK Ab level was 116 nmol/L (normal range, <0.05 nmol/L). Fasciculation appeared in her face and all four limbs after injection of 6 mg edrophonium chloride, indicating hypersensitivity of the neuromuscular junction, previously reported as commonly seen in patients with MuSK-MG [11]. The ice pack test was positive. Repetitive nerve stimulation of the facial nerve at 3 Hz did not show waning. Gadolinium-enhanced thoracic CT showed no thymoma in the mediastinum. Respiratory function tests showed that the

percent vital capacity (%VC) was mildly decreased to 76.3%. She was diagnosed with MG, because she fulfilled the Myasthenia Gravis Foundation of America (MGFA) clinical classification of IIb. She was started on oral prednisolone 10 mg/day every other day and titrated up to a dose of 30 mg/day (Fig. 1a). On day 21 after starting treatment, she showed some improvement in her symptoms, but her nasal voice had not improved much, and her %VC was still decreased at 74.6%. On day 28, double filtration plasmapheresis (DFPP) was performed for 5 days; her nasal voice improved, and her %VC increased to 85.3%. She was discharged on day 40. Three weeks later, anti-MuSK Ab decreased to 10.1 nmol/L, and anti-AChR Ab disappeared (<0.2 nmol/L). After discharge, the prednisolone dosage was tapered; 15 months later, the dosage was 2 mg/day, and no recurrence of symptoms was seen.

Baby's Condition

Her baby was safely delivered by CS at 37 weeks of pregnancy. The Apgar score was 8 at 1 min and 9 at 5 min. Birth length was 48.7 cm, and weight was 2,617 g. Four days after birth, cyanosis appeared when the baby cried, and he developed retractive breathing due to vocal cord paralysis, as seen on endoscopy (Fig. 1b). His serum anti-AChR Ab level was <0.2 nmol/L, and the anti-MuSK Ab level was 19.6 nmol/L. He was diagnosed as having transient neonatal MG (TNMG). He was started on oxygen through a nasal tube. He then gradually improved with only supportive treatment with nasal high-flow therapy and oxygen inhalation. At 45 days after birth, the anti-MuSK Ab level was decreased to 0.69 nmol/L.

Discussion

The present patient was not diagnosed with MuSK-MG during her first pregnancy because her symptoms disappeared spontaneously in the postpartum period. However, her symptoms recurred during her second pregnancy and persisted after delivery, leading to the diagnosis of MG. Treatment with oral steroid therapy and DFPP relieved her symptoms. Her second baby needed intensive care for respiratory impairment due to TNMG. Both the patient and her baby had good clinical outcomes; however, earlier diagnosis is needed to avoid serious conditions such as MG crisis during pregnancy. One noteworthy point is that her first symptom appeared during pregnancy. Eight cases of MuSK-MG with pregnancy have been previously reported (Table 1) [2–4, 6–10]. Similar to the present patient, 6 of 8 patients were first diagnosed with MuSK-MG during pregnancy or the puerperal period. Most of these patients, were delivered by CS, probably due to myasthenic symptoms of the mother. Some of these patients had miscarriages, presumably due to myasthenic symptoms of both the mothers and the babies. These results suggest that female patients with MuSK-MG may have a chance to be diagnosed during pregnancy, and these patients may need to be delivered by CS because of their uncontrolled MG symptoms. It is important to observe symptoms carefully and perform plasma exchange if necessary without delay for symptom control of pregnant MuSK-MG patients, as Kanzaki and Motomura [8] mentioned in their case report. Thus, if the patient develops myasthenic symptoms during pregnancy, anti-MuSK Ab should be evaluated in the early phase.

In terms of TNMG, the present patient's second baby developed bulbar and respiratory symptoms a couple of days after delivery, and anti-MuSK Ab was found in his serum. It is thought that anti-MuSK Ab transferred from the mother through the placenta was the cause

of the TNMG. Previous studies reported that TNMG could occur in 10–15% of cases delivered of MG patients overall [2, 3, 9]. The incidence rate of TNMG from MuSK-MG mothers has never been reported. Previous reports, including the present case, show that 7 of 8 babies developed TNMG [2, 3, 6–10], indicating that the incidence rate of TNMG from MuSK-MG mothers may be much higher than that of anti-AChR Ab-positive MG (AChR-MG) mothers. In the present case, the patient's second baby improved with oxygen, but there were some cases who needed ventilation and intravenous immunoglobulin therapy [2, 7]. Thus, it is important to recognize the higher possibility of TNMG if the mother develops MG, and the baby's condition needs to be carefully observed for at least 1 week after delivery.

In general, there is a 40% chance of exacerbation of MG during pregnancy and an additional 30% risk during the puerperal period [5]. On the other hand, as in the present case, 5 of 8 MuSK-MG patients worsened during pregnancy [4, 7–10]. These findings suggest that MuSK-MG patients are more likely to have exacerbations during pregnancy than AChR-MG patients. Anti-MuSK Ab is classified as IgG4 subclass, whereas anti-AChR Ab is classified as IgG1 and IgG3 [1]. The MG patients carrying anti-MuSK Ab show a tendency towards higher serum levels of IL-4 and IL-10 [12]. Furthermore, a previous in vitro study demonstrated that MuSK-immunized mice had significantly higher levels of IL-4 and IL-10 than those of Freund's complete adjuvant-immunized mice [13], suggesting that IL-4 and IL-10 might play an important role in producing anti-MuSK Ab. During pregnancy, it is known that cytokine levels change for placentation, hCG release, and differentiation. Levels of IL-4 increase throughout normal pregnancy, and levels of IL-10 are increased during the first and second trimesters of pregnancy [14]. IL-10 can act directly on B cells to upregulate IL-4-induced production of IgG4 [15]. Changes in these cytokine levels during pregnancy may raise the anti-MuSK Ab titres.

In conclusion, this case report highlights the fact that female MuSK-MG patients can develop exacerbations during pregnancy, and the baby delivered of a MuSK-MG mother has a high probability of developing TNMG.

Statement of Ethics

The patient provided oral informed consent for publication of this paper.

Disclosure Statement

The authors declare no conflict of interest.

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Author Contributions

Ken-ichi Inoue and Jiro Fukae were the patient's primary physicians, and both performed the review and primary composition of the manuscript. Hiroyasu Kawano was the baby's primary physician. Jun Tsugawa, Shinsuke Fujioka, and Kosuke Fukuhara helped refine the manuscript. Yoshio Tsuboi was involved in the planning and guidance of the written manuscript. All authors were equally involved in the medical management of the patient and approved the final version of the manuscript.

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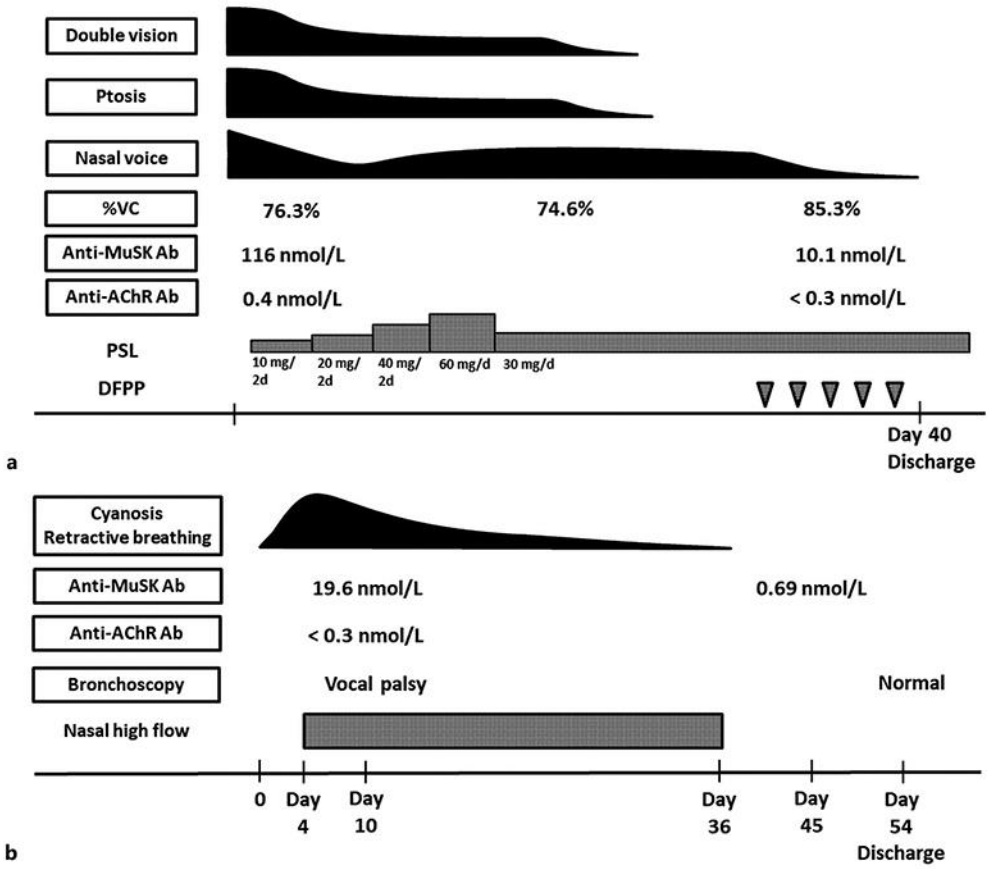

Fig. 1. **a** The clinical course of the mother. **b** The clinical course of the baby.

Table 1. Demographics and clinical features of patients with myasthenia gravis carrying anti-muscle-specific tyrosine kinase antibody and their baby

Case	First symptom	Age at pregnancy, years	Age at diagnosis of MuSK-MG, years	MG symptoms during pregnancy	Treatment during pregnancy	Pregnancy history	Baby delivery/ birth weight	anti-MuSK Ab	symptoms
1 [6]	13 y bilateral ptosis, general fatigue, bulbar palsy, neck paresis	24	23	Steady	PSL 20 mg/2 days	Miscarriage: 2	38 w 1 d/ 3,190 g	+	Difficulty in drinking, hypotonia, weak cry, frog position
2 [2]	22 y bilateral ptosis, double vision, mild facial paresis	26	26 after childbirth	Steady	PSL 40 mg/day		38 w (CS)/ 2,950g	+	Hypotonia, stridor, suckling difficulties (ventilation, IVIg)
3 [7]	29 y transient double vision, general fatigue	30	30 after childbirth	Worsened at 2nd trimester		Miscarriage: 1	34 w (CS)/ unknown	Not examined	Floppy (ventilation, IVIg)
4 [3]	25 y bilateral ptosis	34	32	Steady	Ambenonium, chloride PSL 20 mg –10 mg	25 y (CS); 1st baby: normal	37 w 6 d (CS)/2,558 g	+	Respiratory disturbances, hypertonia of lower limbs
5 [8]	30 y (during pregnancy), bulbar palsy	30	30 during pregnancy	Worsened at 8 months	Pyridostigmine, PSL 10 mg/day, PE		38 w 1 d (CS)/2,482 g	+	Suckling difficulties
6 [9]	27 y (during pregnancy), double vision	27	27 after childbirth	Worsened at 3rd trimester	Pyridostigmine 240 mg/day		37 w 6 d (CS)/2,740 g	Not examined	Hypotonia, respiratory failure (ventilation)
7 [10]	43 y double vision, bilateral ptosis	46	46 during pregnancy	Worsened at 29 weeks	PSL 10 mg/day		30 w 5 d (CS)/1,456 g	+	Respiratory failure (ventilation)
8 [4]	39 y (during pregnancy), bilateral ptosis, double vision, dysphagia	39	39 during pregnancy	Worsened at 15 and 19 weeks	Pyridostigmine 60 mg/day, mPSL 64 mg, IVIg	Miscarriage: 2 (gravida: 3)	34 w 4 d/ 2,360 g	Not examined	Without symptoms
Present case	31 y (during first pregnancy), nasal voice	34	34 after childbirth	Worsened at 12 weeks	Untreated	31 y (CS); 1st baby: respiratory failure Miscarriage: 1	37 w 1 d (CS)/2,617 g	+	Respiratory disturbances, vocal cord paralysis (nasal high flow)

y, years; w, weeks; d, days; PSL, prednisolone; mPSL, methylprednisolone; IVIg, Intravenous immunoglobulin; CS, caesarean section; PE, plasma exchange. The blank part had no description in the text.