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Clinical Short Communication

Intravenous immunoglobulin as monotherapy for myasthenia gravis during pregnancy

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ABSTRACT

Introduction: Pregnant women with myasthenia gravis (MG) are at increased risk of complications and adverse outcomes, including the teratogenic effects of many drugs used to treat MG women of childbearing age. The effectiveness of intravenous immunoglobulins (IVIg) on other autoimmune mediated diseases has been extensively reported in recent years, although little is known about the role of IVIg in the treatment of MG during pregnancy. We designed this study to determine the effectiveness of IVIg as monotherapy during pregnancy for women with MG.

Material and methods: Five pregnant MG patients (mean age at delivery 36.4 years, SD 5.8, range 29.4–45.2) were studied in 2013–14. Their treatment was switched to monthly IVIg cycles 2 months before the pregnancy. Follow-up included monthly neurological QMG throughout the pregnancy and postpartum, obstetrical monitoring during monthly visits in the first two trimesters of the pregnancy, fortnightly visits between week 32 and week 36, and weekly visits after 36 weeks, and neonatal follow-up after delivery.

Results: We observed no exacerbations during pregnancy, delivery or post-partum. The mean QMG score at baseline (before pregnancy) was 7.4 points in five women with generalized forms of MG. The maximum mean value reached during pregnancy was 8.6 points. The mean pregnancy duration was 38 w + 5 d. No infant with transient neonatal myasthenia gravis.

Conclusions: These results suggest that monotherapy with IVIg during pregnancy in MG patients could be promising, although confirmation is required in studies with larger populations.

1. Introduction

Myasthenia gravis (MG) frequently affects young women in the second and third decades of life, overlapping with the childbearing years. Pregnant women with MG have increased risk of complications and adverse outcomes. A clinical exacerbation of the myasthenia, significantly affecting the functional status which may require changes in their medication, occurs in a third of pregnancies (primarily in the first and third trimesters and the postpartum period) [1–21]. Little is known about the causes of these unpredictable complications during pregnancy and the post-partum period. It has been suggested that the disease's exacerbation during pregnancy is unpredictable, albeit more common in the early years of the disease, and there is some controversy as to whether a previous thymectomy could be a protective factor against complications [22]. Physiological changes during pregnancy, including nausea and vomiting in early pregnancy, increased blood volume, changes in renal clearance, and alterations of gastrointestinal absorption, frequently alter the course of myasthenia gravis and may require an adjustment of medication dosages throughout the pregnancy. Furthermore, any pregnancy-associated infection may aggravate the disease.

Because the disease may be exacerbated during pregnancy, over 50% of the women had abstained from having children due to MG. In addition, many of the drugs administered to myasthenic women have teratogenic effects, while others are associated with an increased frequency of miscarriage or low birth weights among newborns [1,4–5,9–10,12–14,16–18,23–26]. Pregnancy does not appear to be an impediment to the use of intravenous human immunoglobulins (IVIg)

Abbreviations: IVIg, intravenous immunoglobulins; MG, myasthenia gravis; QMG, quantitative myasthenia gravis

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[9,12,14,16,17]. Many reports have been compiled in recent years on the use of IVIg in pregnancies affected by other autoimmune diseases [27–30]. IVIg also provides protection from infections and increases the likelihood of pregnancy in women with a history of miscarriage. They are an alternative short-term immunomodulating treatment for myasthenic exacerbations and maintenance of therapy. There is evidence that IVIg are effective, with 70% of MG patients responding with an improvement of at least one grade in the severity of their disease.

Our main objective was to evaluate IVIg as an effective monotherapy for MG during pregnancy, delivery and the post-partum period, based on efficacy measures, including the quantitative myasthenia gravis (QMG) score, improvement or maintenance of the primary symptoms that are most clinically meaningful to the subjects (post-interventional status), and efficacy in preventing antenatal and delivery complications commonly presenting among pregnant MG women.

2. Materials and methods

89 of the 462 patients monitored for MG in our clinic were women of childbearing age (15–49 years old). Of these, five pregnant women (mean age at delivery 36.4 years, SD 5.8, range 29.4–45.2) treated with drugs with a potential teratogenic effect before they became pregnant were studied in 2013–14. The diagnosis of MG was established based on the patient's history, signs and symptoms, EMG (repetitive nerve stimulation and SFEMG), edrophonium test, and serum anti-AChR antibodies. For the patient who was negative for AChR antibodies, the diagnosis was based on clinical findings, EMG, and edrophonium test. The presence of anti-MuSK antibodies was studied in the seronegative patient.

The protocol was designed following the recommendations for clinical research standards of the Myasthenia Gravis Foundation of America (MGFA) [31]. The myasthenic parameters analyzed included MG class at debut, age at debut of MG, quantitative myasthenia gravis (QMG) score for disease severity, treatments, post-interventional status, thymic pathology, antibody titers, concomitant autoimmune diseases, exacerbations and/or previous myasthenic crises. Follow-up of the women took place according to our Myasthenia Gravis Unit protocol, and was carried out by a neurologist, obstetrician, anesthetist and neonatologist. The neurological functional status was measured monthly by the QMG score throughout the pregnancy until 1 month after delivery. The QMG score is a scale ranging from 0 to 39, with higher scores for each of 13 items indicating the most severe weakness. The obstetrician's participation included evaluation prior to conception, monthly evaluations in the first two trimesters, and fortnightly evaluations until week 36 of the pregnancy and weekly visits after the 36th week until delivery. An ultrasound scan was performed in each trimester, except in cases of suspected fetal growth abnormalities. The gestational age at delivery and the type of delivery (cesarean or vaginal) was recorded for each case. The newborns were monitored in the Neonatal Unit for the possible appearance of any of the complications described in newborns delivered from myasthenic mothers, such as low weight, prematurity, arthrogryposis, generalized hypotonia and weakness, and difficulty sucking and swallowing.

Before becoming pregnant, the five women received prednisolone at daily doses of between 25 and 30 mg. In addition to corticosteroids, four also received tacrolimus at doses of 3–5 mg/day. In addition to corticosteroids, one also received a dose of 1000 mg of mycophenolate mofetil. They all also received daily doses of pyridostigmine of 180–240 mg/day. Their treatment was switched to monthly cycles of IVIg (Privigen®; CSL Behring AG, Bern, Switzerland or Flebogamma®; Grifols SL, Spain) when they decided to conceive. The first IVIg infusion was administered 2 months before planning pregnancy. The dosage used was 0.4 g/kg body weight daily for two consecutive days. The infusion rate was 60 ml/h for the first hour, and was subsequently increased to a maximum of 180 ml/h. The patients received the infusion every 4 weeks throughout the gestation period and 1 month post-partum. On confirmation of the pregnancy, the IVIg doses were adjusted to their weight in each infusion. All patients were weaned off their previous oral treatment when they received the first IVIg infusion.

2.1. Statistical studies

Descriptive analysis included age at onset of MG, MG class, QMG sum score for disease severity pre-pregnancy, treatments, post-interventional status, thymic pathology, antibody titers, concomitant autoimmune diseases, exacerbations and/or previous myasthenic crises, time between the diagnosis of myasthenia and conception, duration of pregnancy, highest QMG during pregnancy, and the newborn's birth weight. The continuous variables were expressed as mean ± SD.

2.2. Ethical approval

The protocol was approved by the Clinical Research Ethics Committee (CREC) of the Hospital Universitari Vall d'Hebron on 25 May 2012, with registration number 102/2012(3395).

3. Results

Three women were class IIa, one was class IIb and one was IIIb. Four were acetylcholine receptor antibody positive, and one was double seronegative (AChR-negative and MuSK-negative). The mean time between the diagnosis of myasthenia and conception was 6.2 years (SD 1.9; range 3.1–8.2 years. The women had been thymectomized a mean of 4.1 years (SD 1.6, range 2.5–6.3 years) before the pregnancy. All five presented hyperplasic thymus. All had at least one other autoimmune disease (hypothyroidism in four cases, and one case each of diabetes mellitus type 1, vitiligo and celiac disease). Treatment before pregnancy included large doses of prednisolone, pyridostigmine, mycophenolate mofetil, and tacrolimus. The QMG sum score before pregnancy ranged between 3 and 10 (mean 7.4) (see Table 1).

All the patients except for one conceived in the two-month period after the IVIg treatment began. No significant deterioration of the

Table 1
Patient characteristics before pregnancy.

Case/age at pregnancy (y)	MGFA class	QMG before pregnancy	Serological status	Thymectomy/pathology	Treatment	Other autoimmune diseases
1/28	IIB	10	AChRAb +	Yes/hyperplasia	TAC + PRED + PYR	Hypothyroidism
2/37	IIA	6	AChRAb +	Yes/hyperplasia	TAC + PRED + PYR	Hypothyroidism
3/34	IIA	8	AChRAb +	Yes/hyperplasia	TAC + PRED + PYR	Type 1 DM Hypothyroidism
4/34	IIIB	10	AChRAb − MuSKAb −	Yes/hyperplasia	TAC + PRED	Celiac disease
5/45	IIA	3	AChRAb +	Yes/hyperplasia	MMF + PRED	Hypothyroidism Vitiligo

Abbreviations: TAC = tacrolimus; PRED = prednisone; PYR = pyridostigme; AChRAb = anti-Acetylcholine Receptor autoantibodies; MuSKAb = anti- Muscle-specific receptor kinase autoantibodies.